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BLOOD FORMATION IN INFANCY

PART IV*—THE EARLY ANAEMIA OF PREMATURITY

BY

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(RECEIVED FOR PUBLICATION JANUARY 19, 1955)

In premature infants the post-natal fall in haemoglobin level tends to be exaggerated, so that these infants, although starting life with a cord haemoglobin as high as that of normal infants (see Part III), often develop abnormally low haemoglobin levels during the second month. Usually this early anaemia of prematurity slowly improves from about the fourth month, but is frequently followed by a second phase of anaemia (Fig. 1). This late anaemia of prematurity, which is characterized by hypochromia of the red cells and a response to iron therapy, does not differ from the hypochromic anaemia common in other infants of over 6 months. It reflects the precarious iron balance during infancy, exaggerated by several factors which bear on the premature infant, such as its smaller initial iron stores, its more rapid growth, and its tendency to receive a purely milk diet for a prolonged period. These facts were established many years ago, Mackay (1935) having first clearly distinguished between the early and late phases of anaemia.

The cause of the early anaemia of prematurity has, however, never been precisely understood. Three different mechanisms have been suggested. (1) That the anaemia is the result of an abnormally high rate of destruction of red cells. (2) That it is the result of the rapidity of body growth outstripping a normal erythropoietic capacity. (3) That it is the result of a functional immaturity of the bone marrow, a dyshaemopoiesis.

Each of these three suggested mechanisms will be

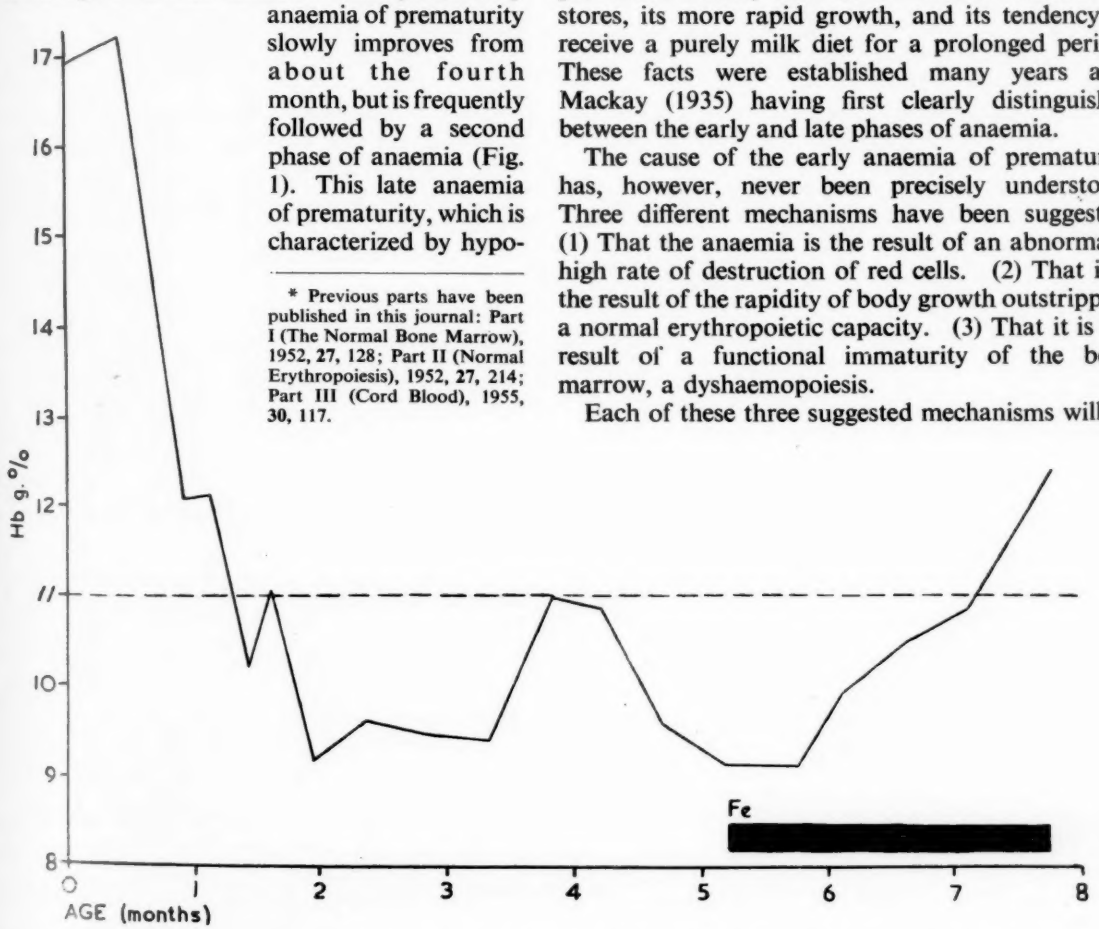

FIG. 1.—Course of haemoglobin level in a premature infant (weight 1,560 g.) from birth to 8 months. Note normal level at birth (cord blood); post-natal fall reaching 9 g. during second month ('early anaemia'); recovery during fourth month, followed by second fall ('late anaemia'). Hypochromia of red cells was present from 4 to 7 months. Iron was exhibited at 5 months with a satisfactory response.

* Previous parts have been published in this journal: Part I (The Normal Bone Marrow), 1952, 27, 128; Part II (Normal Erythropoiesis), 1952, 27, 214; Part III (Cord Blood), 1955, 30, 117.

examined in the light of our data. The consensus of current opinion, judging from paediatric textbooks, is that a combination of these factors operates, and that the early anaemia of prematurity cannot be influenced by giving haematinics. We have arrived at different conclusions.

Material and Methods

Since it is known that the lower the birth weight the more marked is the early anaemia of the premature infant, we have confined our attention to the smaller infant, the 31 infants studied all having birth weights below 1,620 g. (3 lb. 9 oz.). The cord was clamped as soon as conveniently possible after birth. Infants were fed initially on breast milk with vitamin supplements; a few became fully breast fed. The majority, when they reached about 2,000 g. (4½ lb.), were gradually changed on to a cow's milk formula. The dried milk from which this formula was made contained small amounts of added iron and ammonium citrate, such that an infant of 2,000 g. received about 2 mg. iron per day. This formula had long been in use for feeding premature infants, and as it was known that anaemia was not prevented thereby it was decided to continue the established feeding practice. All the infants made uneventful progress.

The main study concerns a group of 26 infants, to half of whom additional iron was given, while another five infants received cobalt as well as iron.

Samples of blood were taken at intervals of one to two weeks beginning as soon as steady weight gain had begun, usually in the second or third week. Venous samples (heparinized) only were employed, up to 1 ml. blood being aspirated, usually from a scalp vein. Venous samples offer the following advantages over skin-prick samples: the falsely high haemoglobin values obtained from skin-prick samples are avoided; measurements can be checked; the haematocrit can be measured and from this the mean corpuscular haemoglobin concentration derived, providing an index of iron deficiency. Haematological methods and in particular standards of haemoglobinometry have been detailed in Part I.

Blood volumes were calculated in order to study changes in the total circulating haemoglobin. Mollison, Veall and Cutbush (1950) and Mollison (1951) give data from which the blood volumes of young infants can be calculated from the body weight and venous haematocrit: the method of using their data has been described in Part I. Mollison *et al.* worked with newborn infants, though they showed that their formula for calculating blood volumes agreed well with accepted values for adults. Nevertheless in applying their data to premature infants, we realize that considerable inaccuracy may result. This point will be taken up again in the following section.

The bone marrow was examined in a number of cases by means of tibial aspiration. From the total count of nucleated cells and the proportion of erythroid cells, the marrow erythroid count was measured. This we have found to be a useful yardstick of erythropoietic activity (see Parts I and II).

The Rate of Destruction of Red Cells after Birth in the Premature Infant

The mean life-span of the red cells of a premature infant can at present only be estimated by indirect means. The fact that neonatal jaundice is often particularly marked in premature infants has often been cited as evidence of haemolysis. Recent studies have not agreed as to whether the degree and persistence of bilirubinaemia is in fact abnormal in premature infants (Obrinsky, Allen and Anderson, 1954; Billing, Cole and Lathe, 1954), but in any case, as Billing *et al.* emphasize, bilirubinaemia in these infants must be largely ascribed to hepatic insufficiency.

There is some evidence (Mollison, 1951) that amongst the red cell population of the full-term infant there may be a small proportion having a somewhat shorter life-span than the 120 days of the normal red cell. It is more than likely that the same applies in the smaller premature infants, some of whose red cells must date from an early period of foetal life. The question is whether such a factor, if it exists, is of sufficient magnitude to contribute significantly to the early anaemia of the premature infant.

In order to gain an answer, even if an imperfect one, to this question, we have estimated the rate of decline of the total haemoglobin during the first few weeks of life in each of the infants of our series. From bone marrow studies to be described later in this paper, it is clear that in premature infants as in normal infants, erythropoiesis is at a low ebb during the first few weeks of life. Therefore it would be expected that the rate of decline of total haemoglobin would be largely determined by the rate of red cell destruction. Suppose the average life-span of the premature infant's red cells to differ little from the normal value of 120 days, then the total haemoglobin present at birth would decline at such a rate that all would have disappeared by the 120th day. By comparing the observed rate of decline of the total haemoglobin with the expected rate, some idea can be gained of whether the rate of destruction of red cells is or is not appreciably greater than normal.

This has been done for an individual infant in Fig. 2. In this case it will be seen that the haemoglobin declined at about the calculated rate during the first month of life. Similar curves were constructed for all 26 infants of the series. In two cases the observed rate of decline of haemoglobin during the first month appreciably exceeded the expected

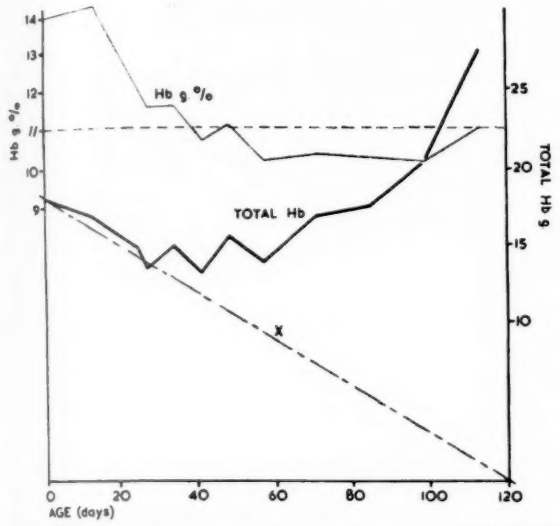

FIG. 2.—Rate of destruction of red cells in a premature infant (weight 1,460 g.). Line X represents the expected rate of decline of total haemoglobin, assuming that new blood formation is negligible and that the mean life-span of the red cells is 120 days. During the first 30 days the observed decline in total haemoglobin proceeded at the expected rate.

rate; in the remaining 24 the observed rate was equal to, or more often considerably less than the expected rate.

The many assumptions implicit in this quantitative approach to the problem obviously make it justifiable to draw only very rough conclusions as to the life-span of the red cells in these cases. We have, for instance, assumed that blood volume comprises the same fraction of body weight in premature as in normal infants, although the scantiness of subcutaneous fat in premature infants presumably means that in them the blood volume actually comprises a somewhat larger fraction. If so, then the total haemoglobin in the early weeks of life will have been estimated too low, and consequently our observed rates of decline of total haemoglobin will be too low. This may explain why the observed rates of decline of total haemoglobin were in some cases less than the expected rate. Nevertheless, after making reasonable allowance for this factor, we conclude that the rate of red cell destruction in the premature infant is unlikely to be much greater than normal, and that therefore excessive red cell destruction is not a major factor in the early anaemia of prematurity.

Since completion of our own studies on this subject, those of Schulman, Smith and Stern (1954) have been published. They have with enviable skill succeeded in measuring blood volumes in premature infants between 1 and 94 days old. Their curve relating blood volume to venous haematocrit in premature infants agrees reasonably well with that given by Mollison (1951) for full-term infants and utilized by us for calculating blood volumes in premature infants. Thus the results of Schulman *et al.* on this point provide support for the validity of our approach.

Rates of decline of total red cell mass were also derived by Schulman *et al.* from their blood volume determinations, and the conclusion was reached that the mean red cell life in premature infants was slightly shorter than normal, with values from 77 to 98 days in contrast to the normal 120 days. These authors finally concluded that while red cell survival in premature infants is probably slightly diminished, this effect is insufficient to account for the production of anaemia, though it may contribute towards it. These conclusions thus differ little from our own.

The Effect of Body Growth

Most thriving premature infants grow nearly as fast as does a foetus of like gestational age; many achieve this standard and not a few surpass it. When the infants of our series reached a weight of about 1,800 g. (4 lb.) the rate of weight gain was usually 1·5–2% per day, such rates being often maintained for several weeks. For comparison, a 2% daily weight gain by an infant of 4·5 kg. (10 lb.) is equivalent to a weekly weight gain of 630 g. (22½ oz.), a rate which is never sustained by a normal infant.

It can be calculated that with a growth rate of 2% per day the daily production of haemoglobin needed to maintain a constant level of 11 g./100 ml. would be 0·14 g./kg. body weight, over and above the amount necessary to replace effete red cells. To maintain the haemoglobin concentration at a somewhat lower level of 8 g./100 ml. would require the daily formation of 0·10 g./kg., i.e., only 70% as much.

It is of interest to compare these figures with some other estimates of the body's capacity to synthesize haemoglobin. For instance, Heath (1933) studied the rate of increase in haemoglobin of a group of adults under treatment with iron for severe hypochromic anaemia: the mean rise of haemoglobin was from 20% to 70% in 30 days. Taking the blood volume of a severely anaemic subject as 60 ml./kg., this rate of rise in haemoglobin concentration is equivalent to a daily increment in total haemoglobin of 0·16 g./kg.

From the data of other authors who have treated severe iron deficiency anaemia in children by means of oral iron (Josephs, 1953), intravenous iron (Dickstein, Wolman, Tan, Slaughter, Butson and Cohen, 1952), or iron and ascorbic acid (Gorten and

Bradley, 1954) values have been similarly derived for the rate of haemoglobin synthesis, expressed as the number of grams of circulating haemoglobin formed per day per kilogram body weight. In these three studies this figure has varied from 0·10 to 0·20 with an average value of 0·15 g./kg.

Such a comparison shows (1) that the growth of the premature infant itself requires the formation of haemoglobin in amounts which are of the same order (in proportion to size) as are produced by the body under the stimulus of iron medication in iron deficiency anaemia; (2) that the lower the haemoglobin concentration in the blood, the smaller the amount of erythropoiesis needed to maintain this concentration during growth. Therefore, if erythropoiesis be insufficient to maintain a normal haemoglobin concentration, the concentration will continue to fall until a level is eventually reached where haemoglobin requirements become balanced by haemoglobin formation.

If rapid growth were the factor mainly responsible for the early anaemia of prematurity, we should expect that the rate of growth would largely determine the degree of anaemia. Accordingly we have assessed the rate of growth in terms of the number of days taken by an infant to double its birth weight, and compared this with the lowest haemoglobin reached. No correlation between rate of growth and degree of anaemia was found. We conclude that rate of growth does not by itself adequately account for the anaemia.

The high rate of growth does, however, necessarily imply that once anaemia has developed in a premature infant from whatever cause, then its correction is likely to be slow. This point is illustrated by the case shown in Fig. 3, where the haemoglobin concentration fell steadily until it reached 8 g./100 ml. on the 58th day. By then erythropoiesis had become active, as shown by the rise in the marrow erythroid count, and the total haemoglobin began to increase. Nevertheless the haemoglobin concentration, on account of the rapid growth of this infant (1·5% per day at this period), fell rather than rose, and from the 80th to the 120th day was still only slowly rising towards a normal level.

We conclude that the rapid growth of the premature infant is not the main cause of the early anaemia, but that it is an important factor in prolonging it.

The Erythropoietic Capacity of the Marrow in the Premature Infant

Our earlier studies of the myelogram in normal infants during the first three months of life (see

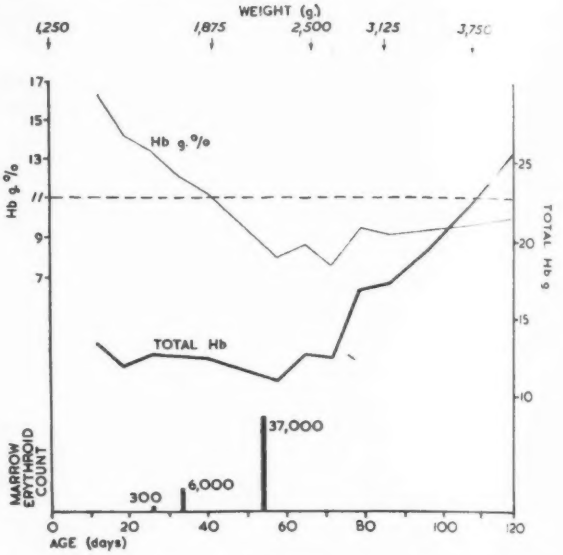

FIG. 3.—Course of total haemoglobin, haemoglobin concentration in g. %, and marrow erythroid count in a premature infant. Note that the erythropoietic activity of the marrow increases only slowly, so that the decline in haemoglobin concentration is not arrested until this has fallen below 9 g. %. From the 60th day the total haemoglobin increases, but owing to the rapid growth of the infant (weight tripled by 110th day) there is only a very slow rise in haemoglobin concentration.

Part II) have revealed a simple pattern. Erythropoietic activity, as gauged by the marrow erythroid count, is high at birth but falls rapidly to a very low level which persists for about two months, by which time the haemoglobin has usually fallen to about 11 g./100 ml. This lowered level stimulates erythropoiesis, the marrow erythroid count gradually rising to a value comparable with that found in normal adults. The lower the haemoglobin falls, the greater the stimulus to the marrow (see Fig. 6 of Part II).

In order to discover whether erythropoiesis follows a similar pattern in premature infants, we have examined marrow samples from infants in our series on 29 occasions, at ages ranging from 26 to 99 days. In 21 instances this examination was made during the second month of life. The marrow has been studied with a view to answering two questions. (1) Do the numbers of the different types of cell and their morphology differ in the premature infant from the normal infant? (2) Does anaemia stimulate erythropoietic activity in the premature as in the normal infant?

The Myelogram in the Premature Infant. We can summarize the results of 29 marrow examinations by stating that we have observed no difference whatever between the morphology of the various

types of cells seen in the marrow of the premature and the normal infant. Megaloblastic erythropoiesis was never seen, and the haemoglobinization and nuclear maturation of the normoblasts followed the pattern seen alike in normal infants and in normal adults.

Two studies of the marrow picture in premature infants have been previously published. Lichtenstein and Nordenson (1939) described various irregularities of maturation of the normoblasts, which (although no normal infants were examined as controls) they interpreted as evidence of a functional insufficiency of the marrow. This work has often been quoted in support of the view that haemopoietic immaturity is the cause of the early anaemia of prematurity, a view for which our findings provide no support. Joppich (1948) examined the marrow of 12 premature infants at ages from 2 to 4 months; he found no sign of abnormal haemopoiesis, the majority of specimens showing active erythropoiesis.

The Erythropoietic Response of the Marrow to Anaemia. By relating the marrow erythroid count to the haemoglobin level of the blood we find that in the premature infant erythropoiesis increases as the haemoglobin level falls, although the response is a sluggish one. An individual case set out in Fig. 3 illustrates this point. The marrow of this infant was examined on three occasions. On the 26th day, when the haemoglobin was 13·4 g./100 ml., the marrow erythroid count was 300/c.mm., showing that erythropoiesis was at a very low level. By the 33rd day the haemoglobin had fallen to 12·1 g./100 ml. and the marrow erythroid count had risen to 6,000/c.mm., still a low count. By the 54th day the haemoglobin had fallen below 9 g./100 ml. and now the marrow erythroid count had risen to 37,000/c.mm. indicating active erythropoiesis, and at the same time the reticulocytes, previously below 2%, rose to 5%. At this point the total haemoglobin started to rise and the fall in haemoglobin concentration was arrested.

A comparable pattern was found in other individual premature infants studied; the erythropoietic response to a falling haemoglobin concentration did not occur until a time lag of some two weeks after the haemoglobin had fallen below 11 g./100 ml. and therefore the fall in haemoglobin was not arrested until levels of 10 g./100 ml. or less had been reached.

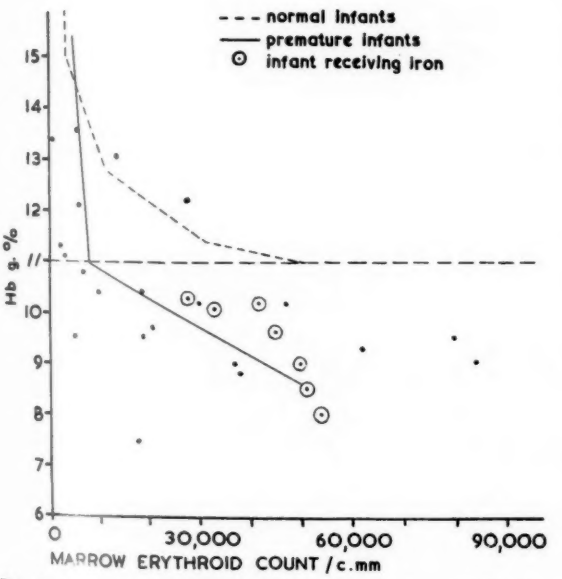

FIG. 4.—Relation of marrow erythroid count to haemoglobin level in blood of premature infants. The unbroken line roughly indicates the trend, which shows that erythropoiesis tends to be at a low level until the haemoglobin falls below 11 g. %. For comparison, the trend in normal infants is represented by a broken line (see text).

The response of the marrow to anaemia is also illustrated in Fig. 4, which shows that there is in general an inverse relation between the marrow erythroid count and the haemoglobin concentration of the blood, the unbroken line roughly indicating the trends of the data for premature infants. The broken line is taken from a comparable series of observations on normal infants (Fig. 6 of Part II). At first sight it appears as if in premature infants erythropoiesis is less sensitive to the stimulus of anaemia, since within the range of haemoglobin 11 to 13 g./100 ml. the marrow erythroid counts tend to be higher in the normal than in the premature infants. This apparent difference can be accounted for by the time lag which elapses between the stimulus provoked by an anaemia and the ability of the marrow to increase erythropoiesis, a delay which means that the more rapid the rate of fall of the haemoglobin level, the lower that level will have reached by the time erythropoiesis increases. Thus the faster rate of decline of the haemoglobin level in the premature infant, occasioned by its rapid growth, exaggerates the effect of the time lag before erythropoiesis mounts.

This time lag is not peculiar to the premature infant, because we have observed the same effect in full-term infants. In two normal infants we were able to study the result of an acute anaemia resulting from a considerable haemorrhage just after birth, such that the haemoglobin was reduced to below 10 g./100 ml. on the first day of life. Erythropoiesis, as gauged by the marrow picture and by the reticulocytes, remained at a low ebb for two to

three weeks in each case, the haemoglobin level consequently continuing to fall during this period. By contrast, an acute post-haemorrhagic anaemia in an adult is known to be followed by a marrow and reticulocyte response within four to six days. The relative insensitivity of the marrow to anaemia seen in the premature infant thus seems to be a general characteristic of early infancy.

The Mechanism of the Early Anaemia of Prematurity

The facts so far presented lead to the following account of the early anaemia of prematurity.

The premature infant, like the normal infant, shows suppression of erythropoiesis shortly after birth. As a result the haemoglobin concentration falls, due to breakdown of red cells at an approximately normal rate. When the haemoglobin approaches a level of 11 to 12 g. erythropoiesis is stimulated, but this stimulus takes some two weeks to produce any appreciable effect in the blood. During this period the infant's haemoglobin level therefore continues to fall, and at a rate which is decidedly faster in the premature than in the normal infant, mainly because of the greater rate of growth of the premature infant. Thus the post-natal fall in haemoglobin is arrested at a level which is well below the normal level of about 11 g. %. The same high rate of growth thereafter makes correction of the anaemia inevitably slow.

It is worth noting that even in normal infants the post-natal fall of haemoglobin may sometimes carry this to levels as low as 9 g. by the seventh week (see Part III), but the lower rate of growth of normal infants allows this anaemia to be corrected quickly.

These views on the mechanism of the early anaemia of prematurity receive further support from the results of giving first iron and secondly cobalt to premature infants.

The Effect of Prophylactic Iron on the Early Anaemia of Prematurity

The effect of iron in the anaemia of prematurity has been the subject of numerous studies, but few of these have made a clear distinction between the effect of iron in the early and the late phase of the anaemia. Merritt and Davidson (1934) found that whether or not premature infants were given iron from shortly after birth, the haemoglobin fell to a level of about 11 g. by the second month, while in the iron-treated group the haemoglobin then tended to rise slowly; in the untreated group it fell further. Comparable results were obtained in a study by Magnusson (1935): in both an iron-treated and a control group the haemoglobin fell to 65% at 11 weeks; thereafter the treated group showed a rapid rise of haemoblobin, whereas in the controls it remained at about 65% over the next three months. Blackfan and Diamond (1944) reached a different conclusion, that iron medication is without influence on the course of the haemoglobin curve at least during the first three months of life. Schulman *et al.* (1954) likewise infer that since about four months elapse before the haemoglobin mass at birth is regained, iron medication is unnecessary before the third or fourth month.

On the assumption that the only purpose of giving iron to premature infants is to prevent iron deficiency developing after the first trimester, the commonest current practice is probably for it to be given only from about the sixth week or later.

In order to clarify the matter we have followed the course of the haemoglobin level in a group of 13 premature infants given iron from shortly after birth, and compared results with those from a control group of 13 premature infants. There are two main differences between this and previous studies. First, only small premature babies (with birth weights below 1,620 g., 3 lb. 9 oz.) have been included, so that results are not diluted by data from larger infants who may never develop anaemia. Secondly, treated and control groups were carefully matched as regards birth weight. In each group there was one case with a weight of 1,000 to 1,200 g., seven cases with a weight of 1,200 to 1,400 g., and five cases with weights of 1,400 to 1,620 g. However, it happened that there were six twins in the treated group and no twins in the control group (see Appendix).

Iron was given as a solution of ferrous sulphate ($FeSO_4$, 7 H_2O) in doses of 60 mg. (1 grain) thrice daily. This was begun during the second or third week. The control group received iron in the same dosage, but starting only after the haemoglobin level had fallen to 11 g., usually at about the sixth week.

Results are shown in Fig. 5. The haemoglobin curves of treated and control groups run together until the 50th day, by which time the haemoglobin has fallen to 10 g. From here the two curves diverge; in the treated group the haemoglobin slowly rises, whereas in the control group it continues to fall, reaching 9·4 g. at the 70th day before starting to rise slowly. Thus between the 50th and 80th days the haemoglobin levels of the treated group averaged 1 g./100 ml. higher than the controls.

The data were analysed statistically (see Appendix); the average haemoglobin level of the treated infants between 60 and 100 days was significantly higher than that of the controls.

The effect of iron can also be seen upon the

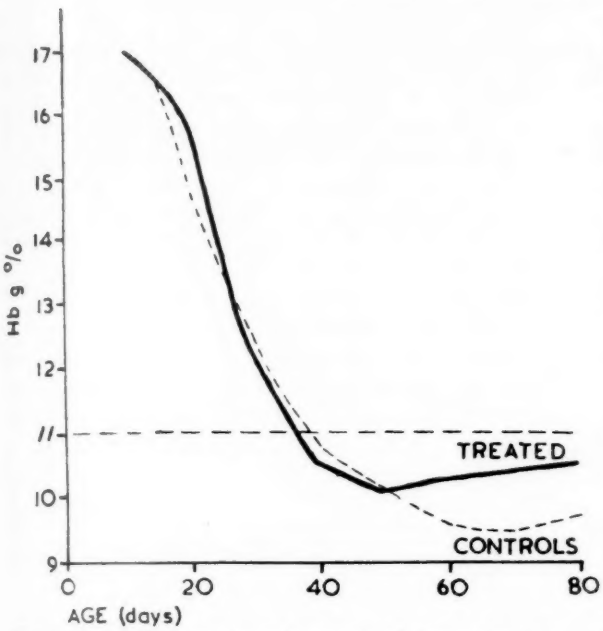

FIG. 5.—Effect of iron on the early anaemia of prematurity. The treated group of 13 infants (birth weights, 1,170-1,620 g.) received iron from about the second week; the 13 controls did not. In the treated group the fall in haemoglobin level is arrested sooner.

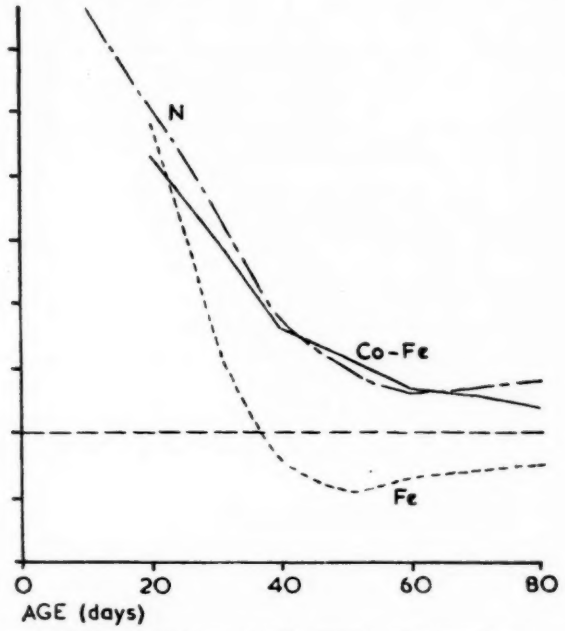

FIG. 6.—Effect of cobalt on the early anaemia of prematurity.
Co-Fe represents five premature infants (weights below 1,530 g.) given cobalt and iron from about the second week.
Fe represents 13 premature infants (weights below 1,620 g.) given iron alone from about the second week.
N is an average normal infant.
The course of the haemoglobin level in the cobalt-treated group is comparable to that of a normal infant.

lowest level to which the haemoglobin fell in the two groups; in four of the 13 treated cases the haemoglobin never fell below 10 g.

LOWEST LEVEL OF HAEMOGLOBIN (G./100 ML.)

	Below 8·0	8·0–8·9	9·0–9·9	10·0+
Treated, 13 cases ..	—	3	6	4
Controls, 13 cases	1	5	7	—

We conclude that iron exhibited from about the third week can, to a small but appreciable degree, mitigate the early anaemia of prematurity. The post-natal fall in haemoglobin level is checked earlier, so that very low haemoglobin levels are less likely to be reached in the third month. The subsequent rise in haemoglobin also occurs earlier, so that treated cases tend to regain normal levels sooner.

The mechanism by which iron produces its effect is obscure. No question of iron deficiency, in the sense of depletion of the body's iron stores, arises as early as the 50th day, the time when the effect of the iron exhibited is becoming apparent, for at this stage the total circulating haemoglobin is usually much less than was present at birth (see Fig. 2). Furthermore, the mean corpuscular haemoglobin concentration has always remained normal throughout the first trimester in the smallest premature infants. From time to time workers in other fields have suggested that iron has a stimulant effect upon haemoglobin synthesis even in the absence of iron deficiency : this is referred to in a recent review by Josephs (1953). As already pointed out, the rapid rate of growth of a premature infant means that haemoglobin synthesis can only exceed by a small margin the amount needed to maintain the haemoglobin concentration constant. It follows that a small increase in the rate of haemoglobin synthesis would have a disproportionately large effect upon the haemoglobin concentration.

The Effect of Cobalt

If we are correct in our conclusion that the main cause of the excessive post-natal fall in the haemoglobin level of premature infants is the slowness of the response of erythropoiesis to the stimulus of anaemia, it follows that the anaemia could be prevented only by causing erythropoiesis to be stimulated earlier and before anaemia has developed. The single agent with claims to possess the property of stimulating the marrow directly is cobalt. We shall not here refer at length to the literature on the haematological effects of cobalt, for this has been

done in recent papers from this country (Coles and James, 1954), the U.S.A. (Rohn, Bond and Klotz, 1953) and Germany (Schmöger, 1953). There is now good evidence that in man as in animals cobalt is capable of stimulating erythropoiesis, although its mode of action remains obscure.

In giving cobalt to premature infants we have combined it with iron, partly on the grounds that if erythropoiesis is to be stimulated it is sensible to provide additional iron for haemoglobin synthesis, partly because we had already shown that iron was itself capable of mitigating the anaemia of these infants. The following mixture has been given:

$FeSO_4$, 7 H_2O	60 mg.
$Co(NO_3)_2$, 6 H_2O	15 mg.
Glucose	0·6 g.
Dilute hypophosphorus acid ..	0·1 ml.
Water to	4 ml.

These amounts, which are equivalent to 12 mg. iron and 3 mg. cobalt, have been given thrice daily to infants irrespective of size, in courses of up to seven weeks.

A group of five premature infants, with birth weights between 1,330 and 1,530 g., were given cobalt and iron from the second or third week, and their blood picture followed in detail.

In general we have fully confirmed the striking effect of cobalt upon erythropoiesis. These effects were usually obvious within one week of exhibiting cobalt. Reticulocytes rose sharply with levels up to 13%, and in some instances normoblasts appeared in very large numbers, up to 7,000/c.mm. These signs of exceptionally energetic erythropoiesis have been the more striking in that they have occurred at a time when the haemoglobin level in the blood was still high, 15 g. or more, when erythropoiesis is ordinarily at a low ebb.

The marrow was examined in three of these premature infants between the 23rd and 37th days when the haemoglobin level lay between 11 and 15 g./100 ml. At this haemoglobin level we should from past experience have anticipated a low level of erythropoiesis (see Fig. 4), yet when cobalt had been exhibited erythropoiesis was active, with the high average marrow erythroid count of 70,000/c.mm. In other respects the myelograms were normal.

The increased output of haemoglobin in the infants given cobalt can be seen most simply by comparing the haemoglobin curves of the group of premature infants treated with cobalt and iron from the second or third weeks, with a group treated with iron alone. Results are shown in Fig. 6, where it will be seen that the cobalt-treated group followed a course closely similar to that of a normal infant, with haemoglobin values well above those of the control group. Since it was found that the cobalt-treated group grew fully as fast as the controls there was clear evidence of increased haemoglobin output in the former.

These results show that by the early administration of cobalt to premature infants erythropoiesis can be stimulated at a time when it is otherwise at a low ebb. In this way the rapid post-natal fall in haemoglobin can be slowed, and the early anaemia of prematurity largely prevented.

Coles and James (1954) have also studied the effect of cobalt on the anaemia of prematurity, observing a large series of infants for up to one year. Their study, although not particularly directed to the early anaemia of prematurity, led them to conclude that cobalt, given in the early weeks of life, was of value in preventing this anaemia. No toxic effects were noted by these workers, using dosages equivalent to 2·5-5 mg. cobalt daily.

Quilligan (1954) gave cobalt in doses equivalent to 10 mg. cobalt daily to 16 premature infants. The treated group showed higher haemoglobin values than the controls, but grew less rapidly.

Toxic Effects of Cobalt. One of the premature infants treated with cobalt developed signs of thyroid disorder. This infant was started on the cobalt-iron mixture on the 13th day, and thrived until aged 9 weeks. The abdomen then became distended with gas and feeds were no longer taken well. A suggestion of exophthalmos was noticeable. A moderately large goitre, 6 cm. in width, became obvious. The cobalt-iron mixture was stopped and within four days the infant began again to feed well and to gain weight. Within three weeks the goitre had disappeared.

On the eighth day, after omitting the cobalt, measurement of radio-iodine uptake by the thyroid gave a value of 38% of the dose. At 72 hours after ingestion of the radio-iodine 2·2% of the dose was present as protein-bound iodine in the plasma. These values lie near the upper range of normal for older children or adults, implying that thyroid function was not at this stage depressed.

Following this episode it was recalled that another infant in the series, who had received cobalt for about six weeks, had developed a mild and transient exophthalmos, although no goitre had been noticed.

Evidence has since come from two further sources that in children and infants cobalt can produce effects upon the thyroid. Gross, Kriss and Spaet (1954) treated children with sickle-cell anaemia giving cobalt in doses of 2·5 to 3 mg./kg./day;

within six to eight weeks three of four children developed goitres with clinical or laboratory evidence of hypothyroidism. McBryde (1954) reported thyroid enlargement developing in a premature infant given cobalt, 5 mg./day, for six weeks.

It is thus clear that cobalt is a potentially goitrogenic agent. Although cobalt given to premature infants will prevent their becoming anaemic, we consider it unjustifiable to expose these infants to the risk of interference with thyroid function.

Summary and Conclusions

The early anaemia of premature infants is due mainly to the slow response of erythropoiesis to the stimulus of anaemia.

This slow response is not peculiar to premature infants, but in them its consequence is exaggerated by the rapidity of their growth.

Rapid growth also has the effect of prolonging the anaemia once this has developed.

There is no evidence that an abnormal rate of red cell destruction, if it occurs, contributes significantly to the production of anaemia.

Marrow studies reveal no differences between the myelograms of premature and normal infants.

Iron, if given from about the third week, mitigates the anaemia but does not always prevent it. Iron is well tolerated and there seems good reason to give it to the smaller premature infants from about the third or fourth week.

If cobalt is given in addition to prophylactic iron, a striking increase in erythropoiesis can be provoked, sufficient in most cases to prevent anaemia developing. However, the effects which cobalt may have upon the thyroid make it unjustifiable to administer it routinely to premature infants.

The nursing care of these premature infants has been the responsibility of Sister H. Brown whose help we gratefully acknowledge.

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APPENDIX

With the assistance of MARTIN J. POLLARD, M.A., B.Sc.

Statistical Analysis of the Effect of Oval Iron on the Haemoglobin Level of Premature Infants

An average value for the haemoglobin level was calculated for each infant separately from observations in the age ranges 40-60 days and 60-100 days.

It happened that there were six twins amongst the 13 treated infants and no twins in the control group. Therefore a statistical analysis was performed comparing the controls with the treated infants, first including the six twins and secondly excluding them.

The following table gives the mean haemoglobin values, the standard errors for those treated and control groups, the corresponding values for 't' and the significance level (P).

	Including Twins		Excluding Twins	
Age range (days)	40–60	60–100	40–60	60–100
Treated Number	13		7	
Mean of average Hb values	10·215	10·418	10·710	10·803
Standard error	0·763	0·687	0·398	0·725
Controls Number	13		13	
Mean of average Hb values	10·097	9·700	10·097	9·700
Standard error	0·912	0·577	0·912	0·577
t	0·358	2·887	1·679	3·733
Degrees of freedom	24	24	18	18
Significance level (P)	>0·1	0·005	>0·05	0·005

The analysis shows that in the age group 40-60 days there is no significant difference between the treated and control groups whether twins are included or not. In the age group 60-100 days the difference is highly significant ($p = 0{\cdot}005$), both including and excluding the twins.

THE SCHÖNLEIN-HENOCH SYNDROME (ANAPHYLACTOID PURPURA) COMPARED WITH CERTAIN FEATURES OF NEPHRITIS AND RHEUMATISM

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 10, 1954)

The aetiology of acute rheumatism and acute nephritis is still not fully understood and even less is known about the Schönlein-Henoch syndrome. Gairdner (1948) drew attention to certain similarities between the Schönlein-Henoch syndrome, acute haemorrhagic glomerulo-nephritis, acute rheumatism and periariteritis nodosa. He suggested that an upper respiratory tract infection associated with the haemolytic streptococcus preceded the first three of these conditions so commonly as to suggest bacterial hypersensitivity as an aetiological factor. He postulated that these conditions were related and that the pathological lesions had a vascular basis.

This study aims at enlarging upon some of the points raised by Gairdner, using large series of cases from southern Scotland.

Material

The cases were admitted to the Royal Hospital for Sick Children, Edinburgh, during the 10-year period 1944-1953, and to the Royal Hospital for Sick Children, Glasgow, during the five-year period 1949-1953. Eight cases of the Schönlein-Henoch syndrome included in the review were from the Western General Hospital, Edinburgh, or Leith Hospital.

Too few cases of periarteritis nodosa occurred to be included in this study. The patients were all under 12 years of age except for a few in their thirteenth year from the Glasgow area.

Method of Selection

All cases of the Schönlein-Henoch syndrome were selected which had the characteristic exanthem and joint and/or abdominal symptoms. Only previously unaffected cases of rheumatism and nephritis were included.

Results

The review is based on 139 cases of the Schönlein-Henoch syndrome, 297 cases of nephritis and 307 cases of rheumatism. The sex ratio of these three conditions is shown in Fig. 1. In the Schönlein-Henoch syndrome group there were 81 males and 58 females, in nephritis 182 males and 115 females and in rheumatism 161 males and 146 females.

The seasonal trends are recorded in Fig. 2. The figures are percentages of the total number of cases of each disease. Fig. 2 shows two peaks coinciding with spring and autumn, but when three-monthly groups of cases are examined a different picture is revealed (Table 1). The Schönlein-Henoch syndrome has a peak incidence in spring and autumn. Rheumatism has a low incidence in the summer months but high totals in spring, autumn, and particularly in mid-winter.

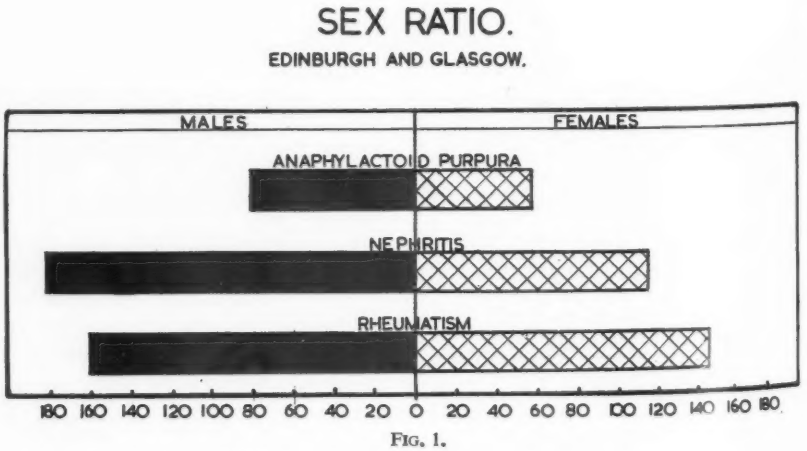

FIG. 1.

TABLE 1
SEASONAL CASE DISTRIBUTION

	March-May	June-August	Sept.-Nov.	Dec.-Feb.
Anaphylactoid purpura	43	23	43	30
Nephritis	69	73	85	70
Rheumatism	77	47	86	97

Nephritis has an even distribution throughout the year except for a slight autumnal rise.

Fig. 3 presents the ages of onset of the three conditions given as percentages of the total number of cases of each disease. The peak incidence of the Schönlein-Henoch syndrome and of nephritis was 4 to 5 years of age and the graphs of the age incidence of these two conditions are remarkably similar. The peak incidence of rheumatism, however, occurs in the age group 7-9 years. Thirty-five per cent of the cases of the Schönlein-Henoch syndrome and 36% of the nephritic cases occurred in the pre-school years compared with only 7% of the rheumatic cases.

The incidence of preceding upper respiratory tract infections and other types of preceding infection together with the organism isolated from the throat swab are shown in Tables 2 and 3. Nephritis was preceded by an upper respiratory tract infection in 179 (60·3%) cases, the Schönlein-Henoch syndrome in 69 (49·6%) cases, and rheumatism in 141 (45·9%) cases. The only other preceding infections of note were scarlet fever associated with rheumatism in seven (2·3%) cases and skin or dental sepsis associated with nephritis in 10 (3·4%) cases. The infecting organism was most commonly the haemolytic streptococcus. It was isolated in 24·3% of the cases of the Schönlein-Henoch syndrome, 19·3% of the rheumatic cases and 22·1% of the nephritic cases. It must be emphasized that these results are derived from the Edinburgh cases only. They are based on routine throat swabs usually taken

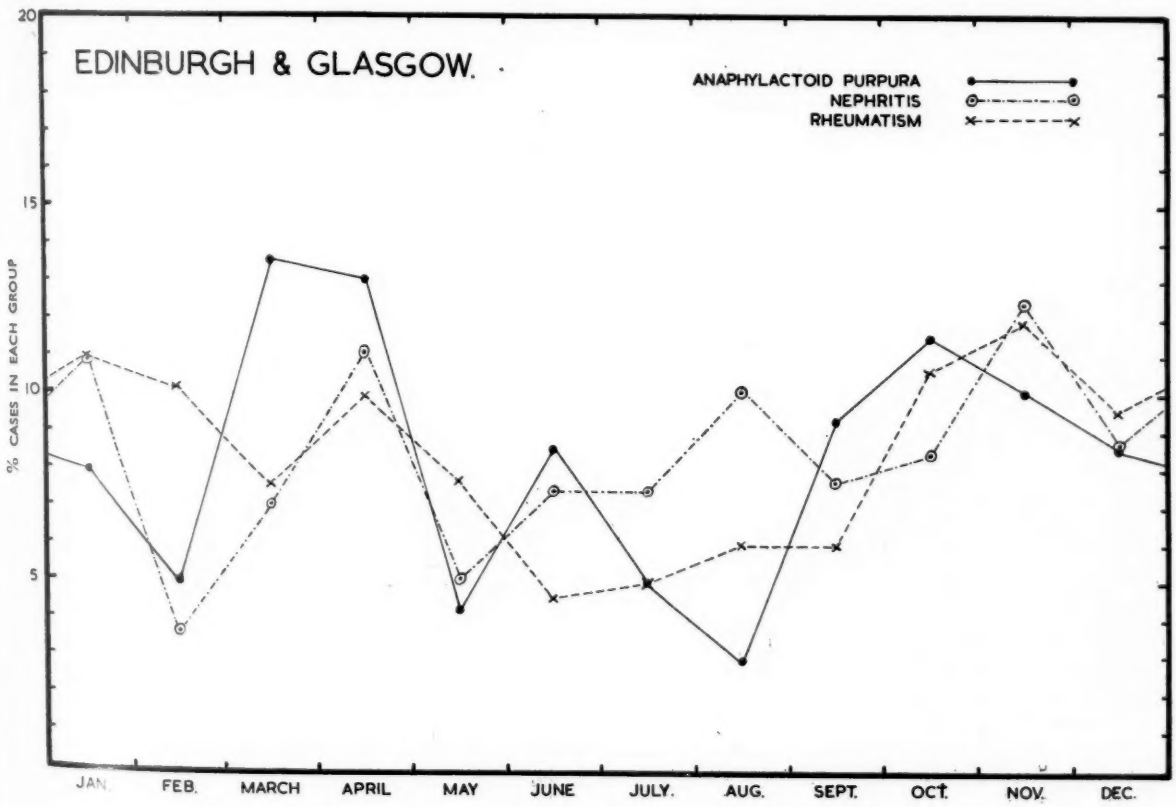

FIG. 2.

TABLE 2
PRECEDING UPPER RESPIRATORY INFECTION (EDINBURGH AND GLASGOW)

Disease	Upper Respiratory Tract Infection	Scarlet Fever	Rubella, Chickenpox, Measles, Mumps	Skin or Dental Sepsis
Anaphylactoid purpura ..	69 (49·6%)	1 (0·7%)	3 (2·2%)	1 (0·7%)
Nephritis	179 (60·3%)	1 (0·3%)	3 (1·0%)	10 (3·4%)
Rheumatism	141 (45·9%)	7 (2·3%)	3 (1·0%)	3 (1·0%)

TABLE 3
THROAT SWAB RESULTS (EDINBURGH CASES ONLY)

Disease	Haemolytic Streptococci	Other Organisms	Not Swabbed	Total Cases
Anaphylactoid purpura ..	17 (24·3%)	35 (50%)	18 (25·7%)	70
Acute nephritis	30 (22·1%)	75 (55·1%)	31 (22·8%)	136
Acute rheumatism	36 (19·3%)	105 (56·4%)	45 (24·3%)	186

after the patient's admission. Repeated and more thorough 'swabbing' might have produced a higher incidence of pathogens.

In some 2,400 routine swabs taken during 1952 and 1953 from the upper respiratory tracts of patients suffering from conditions other than the three mentioned here, haemolytic streptococci were obtained from only 7·3%.

The interval between an upper respiratory tract infection and the onset of the specific disease had a range of from three days to 35 days with an average of 11 days for the Schönlein-Henoch syndrome, and of 12 days for both nephritis and rheumatism. The scattergram (Fig. 4) gives a more detailed picture of the time interval and it clearly demonstrates that in the majority of cases it lay

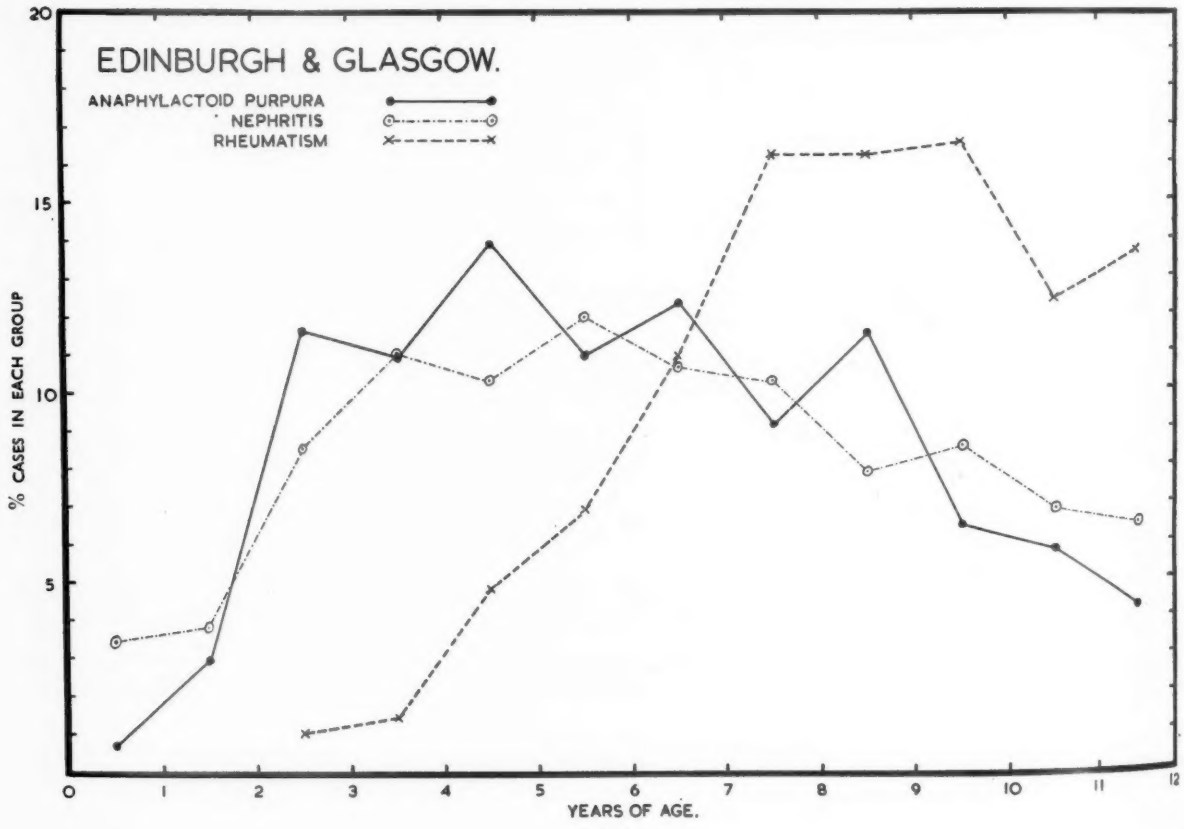

FIG. 3.

between seven and 14 days. In a further 13 (9·4%) cases of the Schönlein-Henoch syndrome, 32 (10·8%) cases of nephritis and 16 (5·2%) cases of rheumatism, an upper respiratory tract infection was said to be present at the time of admission.

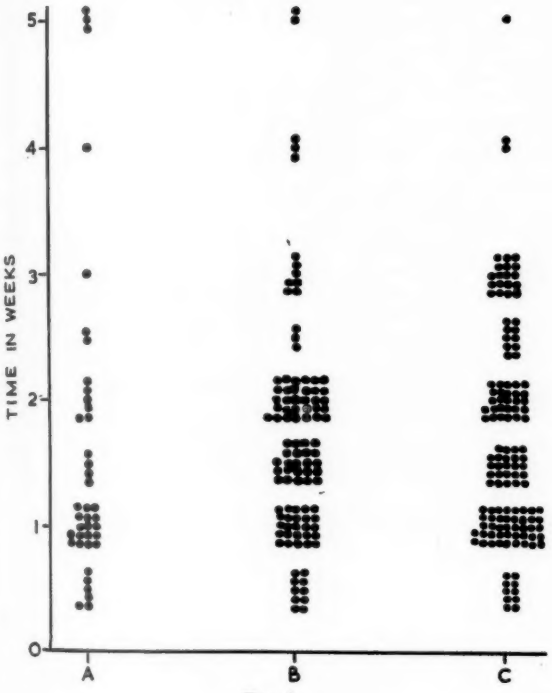

FIG. 4.

A=Anaphylactoid purpura B=Rheumatism C=Nephritis

Discussion

In reports on these three conditions, the relative incidence of aetiological features has varied but no paper has been found giving information gathered from the one geographical area.

The sex ratio in previous reports on the Schönlein-Henoch syndrome are given in Table 4.

TABLE 4
SEX RATIO IN PREVIOUS REPORTS

Authors	Males	Females
Dusch and Hoche (1890)	33	7
Macalister (1906)	5	4
Pratt (1908)	31	12
Gairdner (1948)	10	2
Philpott (1952)	25	15

The present series gives a ratio of approximately 3 males to 2 females and therefore is similar to the figures published by Philpott whose cases were also all children. With regard to nephritis the sex ratio is given as 2 males to 1 female by Goettsch and Lyttle (1951) and by Rubin (1954). Scott (1950) in a large series gave the ratio as 241 males to 134 females. Ellis (1951) states that males predominate but Spence and Davison (1953) describe the sex distribution as equal. The present results give a ratio of approximately 3 males to 2 females. Most investigators agree that in acute rheumatism the sex ratio is equal though Sheldon (1953) states that there is a female predominance of 3 to 2. The present review shows a slight male excess which is similar to the findings of Findlay (1931) in a series of cases from Glasgow. Thus the findings show that in cases from southern Scotland the sex ratios for the Schönlein-Henoch syndrome and nephritis are very similar and that of rheumatism differs considerably.

The seasonal trends are not mentioned in articles on the Schönlein-Henoch syndrome. Rubin (1954) and Goettsch and Lyttle (1951) stated that climate had no effect on the incidence of nephritis in the U.S.A. Chasis (1953) remarked that the incidence was directly related to that of respiratory infections. According to Stollerman (1953) the incidence of rheumatism varies with the country or even with parts of a country. Findlay (1931) stated that it was most common in autumn in Glasgow. The results of the present review show that the Schönlein-Henoch syndrome has a distinct spring and autumn peak and that rheumatism gives a similar picture except that there is a further rise over the winter months. The incidence of nephritis has a slight autumnal rise but there is no great variation in any one season.

The pattern of the age of onset of the Schönlein-Henoch syndrome has not been clearly defined. Gairdner (1948) stated that no typical case had been described under the age of 2 years. Philpott (1952) gave the average age of his cases as 5·2 years with a range of from 8 months to 10½ years. Four of his cases were under 2 years of age. The average age of the 139 cases in the present series was 5·6 years and the range was from 10 months to 12½ years. In all, five cases were under 2 years but the graph showed quite clearly that the commonest age groups for the condition were the 4- and 5-year-olds. Nephritis is regarded as a disease of the young child by Goettsch and Lyttle (1951). Rubin (1954) mentioned that two-thirds of the cases occurred in children under the age of 7 years. Ellis (1951) and Spence and Davison (1953), however, say it is commonest in middle and late childhood. The present review shows that nephritis is commonest in the 4- and 5-year-old groups. Sheldon (1953) states that rheumatism has a maximum incidence in

the 7-, 8- and 9-year-old groups, which agrees with the present findings. Kuttner (1954), however, gives slightly lower figures, namely 6 to 8 years, and Findlay (1931) had most cases in the 7-year-old group in his Scottish series. At the other extreme Scott (1948) found that 12 years was the commonest age in those cases attending the Children's Hospital, Melbourne, Australia.

There are some obvious features which suggest a bacterial hypersensitivity as an aetiological factor in the Schönlein-Henoch syndrome. The high incidence of preceding upper respiratory tract infections, frequently associated with the haemolytic streptococcus, and the similarity between the duration of the latent period before the development of the Schönlein-Henoch syndrome and that for the other two conditions point to such a factor. The sharp rise in the numbers of cases of the Schönlein-Henoch syndrome occurring in the spring and autumn would also suggest a relationship with respiratory tract infections.

Summary

A series of cases of the Schönlein-Henoch syndrome, acute haemorrhagic glomerulo-nephritis, and acute rheumatism have been compared with regard to sex ratio, age of onset, seasonal trends and the incidence of previous upper respiratory tract infections, particularly those associated with the haemolytic streptococcus.

It is suggested that the evidence supports a close relationship between the Schönlein-Henoch syndrome and acute nephritis and a bacterial hypersensitivity as a major aetiological factor in all three conditions.

I wish to thank Professor R. W. B. Ellis, Dr. D. N. Nicholson and Dr. D. M. Douglas for giving me access to their wards and case records. I am also deeply grateful to Professor S. Graham and Dr. J. H. Hutchison of Glasgow, and Dr. J. O. Forfar of the Western General Hospital, Edinburgh, who so kindly allowed me to review the case records of their units.

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THE CLINICAL ASSESSMENT OF HAEMOLYTIC DISEASE OF THE NEWBORN

BY

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From the Research Hospital for Mothers and Children, Prague, Czechoslovakia

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There can be little doubt that at the present stage of our knowledge exchange transfusion is the best method of treating haemolytic disease of the newborn, at least in moderate and severe cases. Recently this viewpoint has been conclusively confirmed by widely based and controlled trials of British workers (Mollison and Walker, 1952; Armitage and Mollison, 1953); their results showed that the mortality of erythroblastotic infants treated by simple transfusions was three times that of those treated by exchange transfusion. In previous years, however, there was a considerable difficulty in differentiating those infants, in whom exchange transfusion was necessary, from those who would not require this radical procedure or any treatment at all. In fact, exchange transfusion is a preventive operation and must be considered soon after birth, i.e., at a time when only severely affected infants show manifest signs of haemolytic disease, most appearing clinically normal. Moreover, the serological findings have appeared to be by no means a reliable index of the post-natal course of the haemolytic disease. The unpredictable prognosis and the relative safety of exchange transfusion made many workers prefer to perform it even in infants who would probably recover without such a procedure. This is not an ideal trend of events and it is obvious that the early and reliable assessment of prognosis in any individual case is essential for the correct treatment.

The available methods of assessing haemolytic disease of the newborn consist of pre-natal control of pregnant women and the examination of newborn infants immediately after birth.

Pre-natally, there are two main points of study: the obstetrical history and the serological findings in the mother.

The occurrence of an adequately proved case of haemolytic disease of the newborn in a sensitized woman is almost always followed by the delivery of a more or less affected infant, unless its blood is compatible with maternal antibodies. Most authors assume that in any one family the prognosis of haemolytic disease gets worse in successive Rh-positive infants. Recently Davies, Gerrard and Waterhouse (1953) suggest, on the basis of statistical analysis, that there are two main groups of sensitized women. One, smaller group, tends to have severely affected infants in all successive pregnancies, and the other group tends to deliver infants with only a mild form of the disease. This observation seems to be in agreement with the frequent finding that in some families several mildly affected infants are successively born without an apparent increase in the severity of the disease. On the other hand, the occurrence of a severe form, i.e., stillbirth, usually signifies an unfavourable prognosis for future births.

The relation between the titre and type of maternal antibodies and the severity of the infant's disease has frequently been studied, and some workers still believe that the level of albumin antibodies is the chief factor determining the prognosis and therefore the treatment (Wiener and Wexler, 1949). There is, however, almost general agreement that the prognostic value of serological findings in the mother is somewhat slight: mothers with a high titre of antibodies have the higher probability of delivering an affected child, but exceptions are frequent and interfere with a reliable prognosis in any individual way.

In summary, at the present time it is not possible to predict the course of haemolytic disease on the basis of prenatal examination or even to prove actual damage of the foetus, with some exceptions, for example, the *x*-ray picture of hydrops foetalis.* The value of antenatal control lies in foreseeing the possibility of the haemolytic affection in the newborn. Thus, at birth all measures to confirm the diagnosis can be ready and adequate treatment undertaken within a few hours of birth.

* Dr. Čech, of our obstetrical staff, has shown that advanced haemolytic anaemia of the foetus is frequently accompanied by a continuous murmur in the foetal heart sounds. This finding in a sensitized pregnant woman can be very useful in deciding delivery before term (Čech, 1953).

After birth haemolytic disease of the newborn can be proved by serological, laboratory and clinical methods.

The finding of blood incompatibility between mother and infant is essential and in 90% of cases the typical combination of Rh-negative mother and Rh-positive child is found. However, the finding of the Rh-identity between mother and infant does not exclude the presence of haemolytic disease of the newborn. The possibility of the blocking effect should be borne in mind, for it means severely affected infants and is probably more frequent than the often quoted cases of incompatibility in Rh-subgroups.

The direct Coombs test is universally accepted as the most sensitive proof of passive immunization in the newborn infant. Its reliability is so high that a positive test can be identified with the presence of haemolytic disease of the newborn. In clinical practice, a negative Coombs test rules out the possibility of haemolytic disease due to Rh incompatibility. On the other hand, it is positive in a certain number of cases without any detectable signs of haemolysis and in mild forms of affection as well. Thus, its value in determining the treatment is to some extent limited.

The aim of laboratory and clinical examination is to prove the basic pathological disturbance, i.e., rapid destruction of red blood cells, and to judge its intensity. As Mollison and Cutbush (1949) have shown, the chief features of abnormal haemolysis, haemolytic anaemia and raised bilirubin level, are present at the end of pregnancy in all cases of haemolytic disease, but they are usually obscured by haemoconcentration and 'physiological' hyperbilirubinaemia of the post-natal period. They stressed the importance of examination of the cord blood.

Mollison and Cutbush (1951) have also shown the close relationship between the haemoglobin concentration in cord blood and the infant's chance of survival. The survival rate falls parallel with the decreasing haemoglobin level, an almost ideal sigmoid curve being the graphical expression. The high prognostic significance of haemoglobin concentration can be adequately explained since this is an index of the anaemic hypoxia to which the foetal tissues have been exposed up to the time of delivery. If permanent damage to vitally important tissues is already present at birth, the fate of the newborn infant can be only little changed by any later treatment.

The bilirubin level is always increased in the cord blood of affected children, but its prognostic significance is not so clear as that of the haemoglobin concentration. Mollison and Cutbush (1951) suggest that the prognosis cannot be more accurately predicted from haemoglobin and bilirubin concentrations together than from haemoglobin level alone. This conclusion is undoubtedly correct, if we consider the simple prediction of death or survival in a series of adequately treated children. Nevertheless, an increase of the bilirubin level in cord blood indicates an increased rate of destruction of red cells and the likelihood of the newborn infant being affected by severe hyperbilirubinaemia and perhaps developing kernikterus. This potential danger is usually prevented by exchange transfusion and the real prognostic significance of hyperbilirubinaemia is thus obscured. Nevertheless, it may be very useful in deciding on the necessity of exchange transfusion in borderline cases, where the haemoglobin concentration alone is not an entirely reliable guide (Mollison and Cutbush, 1951).

The assessment of a case is completed by the usual clinical and haematological examination. Definite anaemia in the capillary blood confirms the haemolytic process, when other causes of anaemia, for example, bleeding, are excluded. An increased number of nucleated red cells strongly supports the diagnosis of haemolytic disease of the newborn. Pallor, hepato- and splenomegaly and early deep jaundice are the common clinical signs of the disease. The assessment of a case in which the examination of the cord blood has been omitted is based on these far less reliable features.

The Present Series

All pregnant women registered with the pre-natal clinic of the Research Hospital in Prague were tested for blood grouping, and Rh-negative patients were followed throughout pregnancy for the development of antibodies. The condition of every isoimmunized woman was analysed before and after birth by the methods described, but the final decision as to prognosis and treatment was based on the estimation of the haemoglobin and bilirubin concentrations in the cord blood.

Haemoglobin was determined by drawing 0·25 ml. of cord blood by pipette into 5 ml. of 0·1% $NaCO_3$. The resulting solution of oxyhaemoglobin was read in a Leitz photometer using a green filter (Nr. 550). The method is very simple and reliable and is the usual method of haemoglobin determination in our hospital.

Serum bilirubin was determined using a modification of the usual diazo method without caffein.

The normal range of haemoglobin and bilirubin concentrations was determined in the cord blood samples of 150 normal newborn infants. The mean

haemoglobin concentration was 16·06 g./100 ml. (S.D. 1·43 g./100 ml.). Values below 12 g./100 ml. were considered definitely abnormal. The mean bilirubin concentration was 1·68 mg./100 ml. (S.D. 0·5 mg./100 ml.), the level of 3 mg./100 ml. being considered the upper limit of normal values. At the beginning of our work levels of 11·5 g. haemoglobin and 4 mg. bilirubin were assumed to be borderlines of normal values, but this opinion was corrected by further experience.

In our series are included 114 clearly isoimmunized women, observed from May, 1950, to May, 1954. Women without conclusive proof of isoimmunization, i.e., those with only traces of antibody or with a transient finding of low titre antibodies, especially during the first pregnancy, were excluded.

The values of cord haemoglobin and bilirubin concentration of newborn infants are plotted against one another in Fig. 1. The values of Rh-negative infants are excluded for the sake of clarity.

In the series 29 Rh-negative newborn infants were born. Of the group of Rh-positive children, exchange transfusion was not performed in 39 infants: eight infants were so severely affected that they died before any treatment could be started. Three infants developed mild neonatal anaemia, requiring only simple transfusions, and 28 infants showed no signs of disease. Forty-six newborn infants were treated by exchange transfusion. There were 41 survivors and five infants died, the mortality being 12·5%.

All surviving infants were followed during their stay in hospital and subsequently either by direct examination or by letter at longer intervals. One infant developed hydrocephalus with motor and mental retardation, but the relationship to haemolytic disease of the newborn is doubtful. The other cases showed neither features of kernikterus in the neonatal period nor signs of permanent damage to the central nervous system later. These favourable results are in rather sharp contrast to statements of other workers and can be explained by two facts. (1) In our series, premature induction of delivery was almost entirely abandoned, only one infant being below 2,500 g. birth weight. (2) The development of deep jaundice was prevented by exchange transfusions repeated if necessary.

Another point of interest is the unusually high incidence of Rh-positive children without signs of haemolytic disease of the newborn. It is probable that this finding is due partly to the fact that the more reliable clinical assessment of individual cases has allowed us to be conservative with some infants that otherwise would be treated more actively.

This series of 114 infants is not entirely representative of our whole material seen during the quoted period. Cases not adequately controlled, i.e., infants born in other obstetrical centres and transferred later to our hospital or those from whom samples of cord blood were not obtained, were excluded from the present series. The total number of exchange transfusions carried out up to May, 1954, was 103 with 13 deaths.

Infants of isoimmunized women can be divided into four groups, approximately separated by the limits of normal values of haemoglobin and bilirubin as shown in Fig. 1.

(1) The haemoglobin concentration is normal or mildly decreased, and the bilirubin level does not exceed 3 mg./100 ml. All Rh-negative infants belong to this group, and in addition a certain number of Rh-positive ones without signs of haemolytic disturbance, though the Coombs test is often positive. At the borderline of haemoglobin values cases occur with a mildly increased rate of red cell destruction without deep jaundice, thus forming the picture of haemolytic anaemia. In infants with a negative Coombs test, the antibodies probably did not pass the placental barrier and the presence of haemolytic disease of the newborn is thus excluded.

(2) The haemoglobin concentration is the same as in Group I, but the bilirubin level is increased. Apparently disintegration of red cells is abnormally rapid, but foetal anaemia has not yet reached a significant degree, either because haemolysis has not been of long duration or because of sufficient compensation by increased blood production. The prognosis is good for the tissues are not damaged by previous anaemia, but the infant is threatened by severe hyperbilirubinaemia and exchange transfusion is necessary.

(3) The haemoglobin concentration is low (below 12 g./100 ml.), the bilirubin concentration increased—typical haemolytic disease with more or less advanced anaemia, the degree of which indicates the prognosis for the infant. Immediate radical treatment is necessary. Exchange transfusion, in severe cases carried out with special caution, is the best therapy.

(4) The haemoglobin is lowered, the bilirubin concentration within normal limits. As shown in the diagram, such cases are rare in practice and mean theoretically foetal anaemia of non-haemolytic origin. Wiener (1948) described such anaemias from latent bleeding in complicated pregnancies, for example, placenta praevia. Simple transfusion is the only treatment required.

It is interesting that the most severe cases presenting as hydrops foetalis exhibit, besides an extremely

low haemoglobin level, a low concentration of cord bilirubin. It is difficult to say whether the cause of this phenomenon is exhaustion of haemoglobin stores, failure of bilirubin-producing tissues or perhaps advanced changes in distribution of body fluids.

The great variability of haemolytic disease of the newborn is clearly shown by this grouping. There is a wide and gradual transition from the infants of Group 1, in whom the presence of the haemolytic process is indicated only by laboratory proof of passive immunization of the foetus, to the total failure of bodily defences in the hydropic foetus of Group 4.

Discussion

The fact seems to be well established that the

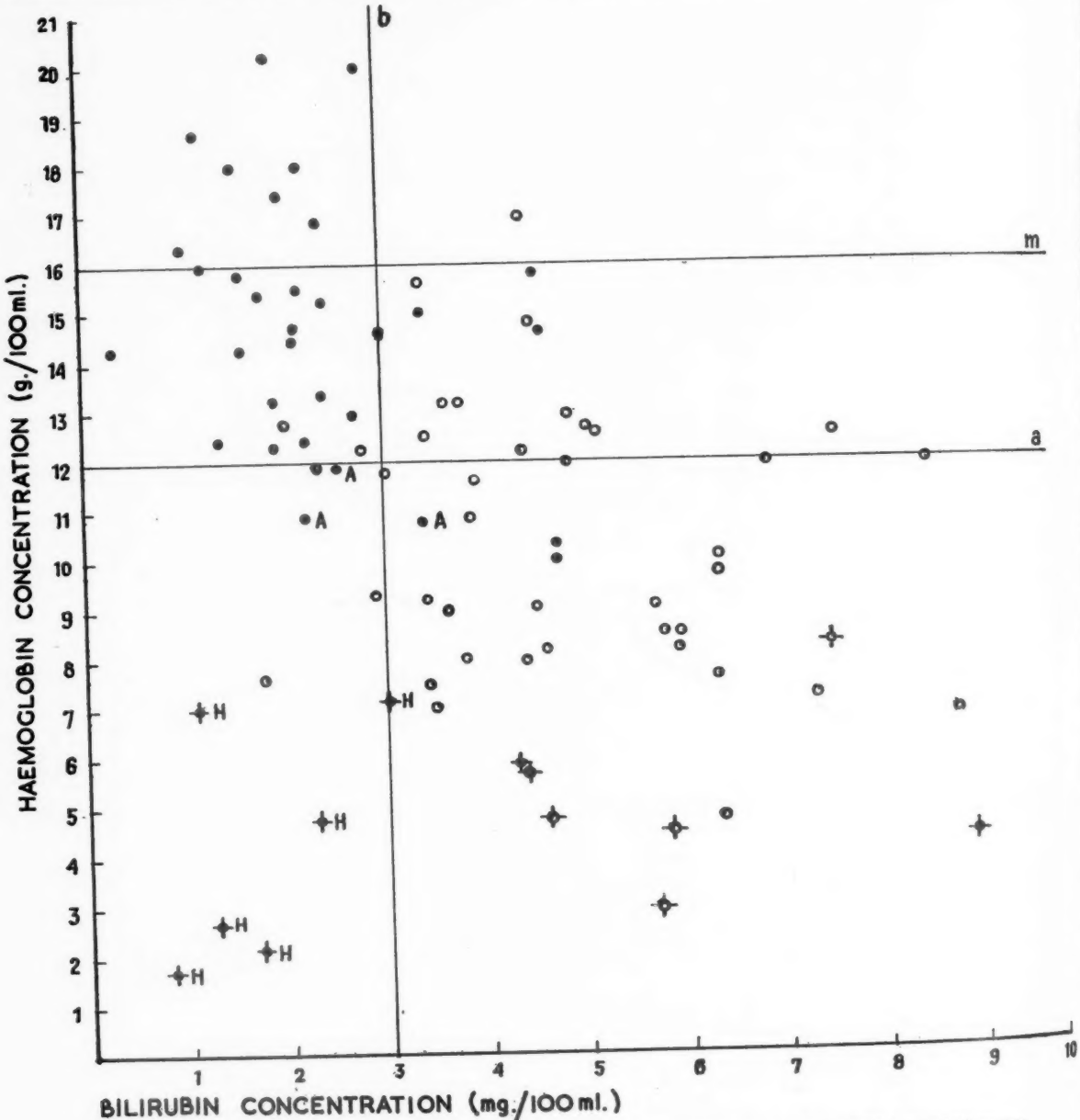

FIG. 1.—Cord haemoglobin concentration plotted against cord bilirubin concentration in infants of Rh-immunized women. ● Cases not treated by exchange transfusion. ○ Cases treated by exchange transfusion. -⊙- Deaths, -✦- H Hydrops foetalis. ● A Haemolytic anaemia of the newborn.
Lines a and b are limits of normal values, line m is the mean haemoglobin concentration.

foetus of an isoimmunized woman is threatened by two different pathological conditions.

Severe haemolytic anaemia is the usual mechanism of death *in utero*. A small number of severely anaemic infants are born still alive but die within 24 hours of birth. In cord blood an extremely low haemoglobin level is found, usually below 6g./100 ml., and a fall to the level of 4 g./100 ml. means a hopeless outlook. Congestive heart failure is probably the immediate cause of death, as indicated by the raised venous pressure in the umbilical vein. There is little hope of saving these children, but occasionally a seriously affected infant can survive.

A.V., aged 24 years, a three-gravida, was group A Rh-negative, with Rh-antibodies in albumin at a titre of 1 in 32+. Her first child was normal, the second child died on the fifth day of icterus gravis. On March 5, 1953, she was delivered of a girl (birth weight 3,000 g.). The infant's blood group was A Rh-positive. The Coombs test was ++. The baby's general condition was very poor; she was pale, subicteric, with oedema of the face and legs and numerous petechiae of the skin. In the cord blood haemoglobin was 4·7 g./100 ml., bilirubin 6·3 mg./100 ml., and plasma proteins 3·9 g./100 ml.

The first exchange transfusion was given nine hours after birth when 300 ml. of blood was replaced. The second exchange transfusion was given 33 hours after birth and 400 ml. blood was replaced, a total exchange of 80%. The general condition remained rather poor for three weeks with loss of 21% weight and rather deep jaundice. Then her condition slowly ameliorated; the serum proteins rose to 4·9 g./100 ml. The further course was uneventful. During frequent follow-up until the present time the child appears to be mentally and physically entirely normal.

The other mechanism of death may be designated endogenous intoxication and means the failure of vitally important functions due to the toxic effects of the products of red cell destruction. This toxic stage threatens newborn infants who have escaped death from haemolytic anaemia and takes place in the period of severe hyperbilirubinaemia, i.e., within two to five days of birth. The newborn child is apparently inundated by bilirubin, the end-product of haemoglobin disintegration; there is no proof that the other products of haemolysis, potassium or porphyrins, collaborate in causing the failure of the infant's organism.

The immediate cause of death is damage to the regulating and coordinating function of the central nervous system (failure of medullary centres) and its morphological expression is biliary staining of brain tissues. The genesis of kernikterus is not yet entirely settled and some workers still believe that bile staining of the basal ganglia is secondary to injury of the nerve cells by some other factor, i.e., by anoxia or direct activity of Rh-antibodies. Recently, however, evidence has slowly been accumulated that kernikterus is really the sequel of severe hyperbilirubinaemia, the physiological immaturity of the neonatal period being the other necessary condition of its development. This opinion is supported by two groups of observations.

The development of kernikterus is not specifically confined to the presence of haemolytic disease. The non-specific character of kernikterus was demonstrated by Zuelzer and Mudgett (1950), who found it at necropsy in a group of infants without any clinical and serological features of haemolytic disease of the newborn. As the cause of death, a heterogeneous group of pathological conditions was found, the most striking finding being prematurity in 70% of cases. Similarly Aidin, Corner and Tovey (1950) showed a rather high incidence of kernikterus in premature infants in whom the presence of haemolytic disease of the newborn could be excluded and this observation has been confirmed by many authors. Kernikterus has also been found in a group of children suffering from chronic, non-haemolytic jaundice, probably on the basis of congenital insufficiency of the liver to excrete bilirubin (Crigler and Najjar, 1952). Although these observations are sometimes interpreted by their authors in a controversial way, at least they can exclude the assumption of the directly injurious effect of Rh-antibodies as the chief cause of kernikterus.

Even more important is the fact that the development of kernikterus is closely related to the severity of post-natal bilirubinaemia. The common observation that the kernikterus occurs always in deeply jaundiced infants has been recently confirmed more precisely. Hsia, Allen, Diamond and Gellis (1952) showed by estimation of the post-natal curve of bilirubin that kernikterus is not likely to develop when the bilirubin concentration does not exceed 20 mg./100 ml., but its incidence rises sharply with increasing bilirubin, reaching 50% in cases above 30 mg./100 ml. Likewise, Mollison and Cutbush indicate 18 mg./100 ml. as the limit of maximum bilirubin concentration within which infants are not threatened by kernikterus. This quantitative connexion strongly supports the supposition that the hyperbilirubinaemia plays the primary part in the genesis of kernikterus.

There is some controversy about the part anaemia plays in the development of kernikterus. Diamond suggested that the incidence of kernikterus is independent of the degree of anaemia. On the other hand, Armitage and Mollison (1953) found a

significantly greater incidence of kernikterus in infants with low cord haemoglobin concentrations. However, anaemic infants clearly show a tendency to have a higher concentration of cord bilirubin. In our series, the relationship of the mean bilirubin values to the cord haemoglobin concentration was as follows:

Haemoglobin Concentration (g.%)	Mean Bilirubin Concentration (mg.%)	Difference (mg.%)
Above 15	2·35	1·28±0·38
10·1–15	3·62	1·65±0·43
Below 10	5·24	P<0·01

It is apparently possible to explain the relationship of anaemia to the genesis of kernikterus by its association with hyperbilirubinaemia. Nevertheless, the possibility cannot be excluded that the development of kernikterus is supported by the non-specific influence of any kind of anoxia (anaemic, anoxic, by shock), i.e., by increasing the penetrability of cerebral vessels and nerve tissues to bilirubin.

These facts show that the assessment of post-natal hyperbilirubinaemia is essential for a correct decision as to therapy after birth. Ylppö, Davidson, and other workers found the relationship between the concentration of foetal bilirubin and the subsequent intensity of bilirubinaemia of the newborn: the higher the concentration in the cord blood, the higher usually is the maximum of the serum bilirubin curve within the first days after birth. Although more recent papers (Findlay, Higgins and Stanier, 1947; Hsia *et al.*, 1953) show a greater variability, it is generally agreed that the cord blood bilirubin concentration almost never exceeds the level of 3 mg./100 ml. and its subsequent rise does not reach dangerous heights in normal, full-term, newborn infants. The conclusion is justified and confirmed by experience that a cord bilirubin concentration above 3 mg./100 ml. in newborn infants with serological findings compatible with haemolytic disease of the newborn indicates subsequent high bilirubinaemia and the danger of kernikterus.

Obviously, a certain number of infants with a cord bilirubin concentration just above 3 mg./100 ml. would not develop kernikterus even without any treatment, but one cannot differentiate these cases. The quantitative conditions of formation and excretion of the bilirubin in the foetal and neonatal period are poorly understood and the real height of the bilirubin curve after birth is only roughly predicted by the cord bilirubin level. Moreover, the fate of an affected infant is to a great extent determined by its individual susceptibility to kernikterus, which is highly variable and unpredictable.

We feel that an adequate margin of safety is given by setting 3 mg./100 ml. as the limit of cord bilirubin concentration for introducing therapy to prevent abnormal increase in bilirubinaemia. In full-term infants this assumption has been fully confirmed by our experience of the last four years, although values below 3 mg./100 ml. have occasionally been seen in the cord blood of erythroblastotic* infants by other workers (Hsia, Allen, Gellis and Diamond, 1952).

In premature infants the estimation of suitable therapy must be made more cautiously. As recently shown by Hsia *et al.* (1953), the post-natal rise of the bilirubin curve is higher and longer in premature infants in physiological conditions, although the foetal bilirubin is not elevated and may even be decreased (our findings). There is no doubt that in premature infants with a tendency to abnormal red cell destruction bilirubinaemia can reach dangerous heights even when the cord bilirubin concentrations do not exceed normal limits.

It is our rule to perform exchange transfusion in newborn infants of isoimmunized mothers (1) when the haemoglobin in the cord blood is below 12 g./100 ml., in which cases the bilirubin level is almost invariably increased; (2) when the haemoglobin is above 12 g./100 ml. and the cord bilirubin concentration exceeds the limit of 3 mg./100 ml.; (3) in premature infants a more individual and cautious decision is necessary. It seems reasonable to carry out exchange transfusion in every premature infant with a positive Coombs reaction.

As shown by Fig. 1, the common factor of all cases of haemolytic disease of the newborn requiring exchange transfusion is the high concentration of bilirubin in the cord blood. Many workers are satisfied by the estimation of cord bilirubin alone as the index of the necessity for exchange transfusion. This is of some advantage since the bilirubin level can be estimated subsequently in coagulated blood when samples of fluid blood for haemoglobin estimation are not obtained. The prognostic value of the haemoglobin concentration is, of course, not diminished.

We consider the combined estimation of the haemoglobin and bilirubin concentration in the cord blood the most reliable guide in the treatment of haemolytic disease of the newborn and we use the other tests only as auxiliary methods, i.e., in poorly followed cases.

Summary

Common methods of assessing the severity of haemolytic disease of the newborn, before and after

* No data are given, however, on criteria of diagnosis and severity of haemolytic disease of the newborn in these children.

birth, are briefly discussed. Haemoglobin and bilirubin concentrations in cord blood are taken as the chief criteria of severity. Exchange transfusion is performed (1) when the cord haemoglobin concentration is below 12 g./100 ml.; (2) when the haemoglobin is above 12 g./100 ml. and the cord bilirubin concentration exceeds 3 mg./100 ml; (3) when the Coombs test is positive in premature infants. By these criteria, exchange transfusion was indicated in 46 newborn infants (five deaths, no case of kernikterus in survivors). On the other hand, their reliability has allowed a conservative attitude to be taken without any harm in 31 Rh-positive infants of isoimmunized mothers.

Some problems of the pathogenesis of icterus gravis and kernikterus are discussed.

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THE DENTAL CHANGES ASSOCIATED WITH KERNIKTERUS

BY

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It is widely recognized that children who have recovered from haemolytic disease may show green pigmentation of the deciduous teeth. Marsland and Gerrard (1953) have described the condition fully, and the pigment has been identified as biliverdin by Bevis (1954).

The dental changes which are associated with kernikterus have received less attention. Only two references to this subject have been discovered. Koupernik and Buhot (1952), without describing a specific case, mentioned the occurrence of a crescent-shaped erosion of the teeth in kernikterus. Kölbl and Rosenkranz (1952) described two cases showing green pigmentation and enamel hypoplasia. All these authors referred to kernikterus following haemolytic disease.

It is the aim of this paper to describe these dental changes in more detail and to draw attention to their significance.

History and Scope of the Investigation

During a recent review of children who had recovered from haemolytic disease of the newborn several with the typical green teeth were examined. (One of these has been reported previously by Miller in 1951.) It was noted that in no case was there any clinical evidence of kernikterus.

As both green teeth and kernikterus appear, in general, to be manifest in the more severely jaundiced cases of haemolytic disease this finding seemed curious.

Further evidence of the dissociation between green teeth and kernikterus was sought in the literature on dental pigmentation. In the cases recorded by Thursfield (1912), Losch, Brown and Boyle (1940), Boyle and Dinnerman (1941), Parsons (1947), Pickles (1949), Stones (1951) and Tank (1951), there was no mention of the physical or mental state of their patients; Craig (1925), Ellis (1938), Nickerson and Moulton (1943), Potter (1947) and Farquhar (1951), however, recorded their patients as normal, apart from the dental pigmentation. MacRae (1952) described his one patient as normal apart from nerve deafness, but in the light of subsequent knowledge this symptom may well have been an isolated manifestation of kernikterus. Marsland and Gerrard (1953) made no reference in their paper to the general state of their patients, but Gerrard (1954) has stated that three of their 17 cases (Nos. 1, 4 and 6) showed evidence of kernikterus.

In view of these conflicting reports it was decided to review all available cases of kernikterus. Thirteen children were examined: no dental pigmentation was found, but enamel hypoplasia was present in the deciduous teeth of every one. These cases, where kernikterus followed haemolytic disease, will be described as Group I.

While this review was in progress one of us was following up all the known cases of retrolental fibroplasia from two premature nurseries in Manchester (Forrester, Jefferson and Naunton, 1954). Similar dental lesions were discovered in several children who had both retrolental fibroplasia and cerebral palsy. These cases, together with certain others in premature infants, are described separately (Group II).

Note on Enamel Hypoplasia

Enamel hypoplasia is generally regarded as originating in metabolic disturbances which interfere with the activity of the enamel organ. Minor hypoplastic lesions, such as localized opaque areas in the tooth substance, have been described by many writers; in more severe cases the enamel becomes 'pitted'. In teeth seriously or extensively hypoplastic there is either marked thinning or apparent absence of the enamel in the affected area.

For the purpose of this paper the minor forms of enamel hypoplasia have been disregarded, and the following descriptions apply to the condition reported:

'Mild' denotes discrete pitting of the enamel of the crown of the tooth, 'severe' the coalescence of

pits to form lines or rings, areas of tooth crown sometimes apparently devoid of enamel.

The site of the hypoplastic area on the crown of a tooth is related to the age at which metabolism was disturbed. Each tooth begins to form at the cusp and grows to form first the crown and later the root. The approximate state of development of the teeth in relation to age is shown in Fig. 1. It will be seen that the incisors are the first teeth to begin to form and are followed by the canines and molars. Thus, a metabolic disturbance at a date corresponding to the seventh month of intrauterine life would be expected to affect the incisor teeth half-way through their development, but would only touch the tips of the canines and molars. A disturbance at or about full-term would be likely to affect the teeth at a later stage of their development and the enamel lesions would appear nearer the gum margin.

Group I : Kernikterus Following Haemolytic Disease

In this group 13 children with known kernikterus were examined; all showed enamel hypoplasia. There was slight variation in site and considerable variation in severity between children, and in many cases the original lesion appeared to have been modified by attrition or caries. Despite these modifying factors the lesions were easily recognized on the canine teeth as a 'notch' where the layer of enamel suddenly became thinner (Fig. 2). In some cases this notch was detectable only on the buccal surface of the tooth, but often it appeared as a complete 'ring' around the crown. Both the 'notch' and the 'ring' lesions were readily palpable. These 13 cases were so similar medically and dentally that it is not proposed to describe each in detail. In 12 there was a clear history of haemolytic disease due to Rh incompatibility. In the thirteenth there was haemolytic disease due to ABO incompatibility. This last case and several others showed special features which do, however, merit detailed description.

Case 1 (P.H.). This child, a boy, was one of monovular twins. The mother was Rh negative with strong antibodies. She had had four previous pregnancies: the first three children had been normal but the fourth had died of haemolytic disease on the third day of life. Delivery took place one week before the estimated date. The twin (P.H.) who is the subject of this report had a birth weight of 6 lb. 8 oz. The Coombs test was positive. The haemoglobin of the peripheral blood shortly after birth was 92%; jaundice was apparent within the first 12 hours of life. He was thought to be mildly affected and no exchange transfusion was done. He rapidly became deeply jaundiced, feverish and drowsy and developed neck stiffness. The jaundice took many weeks to subside, but there was never any serious degree of anaemia and no transfusions were needed. By the

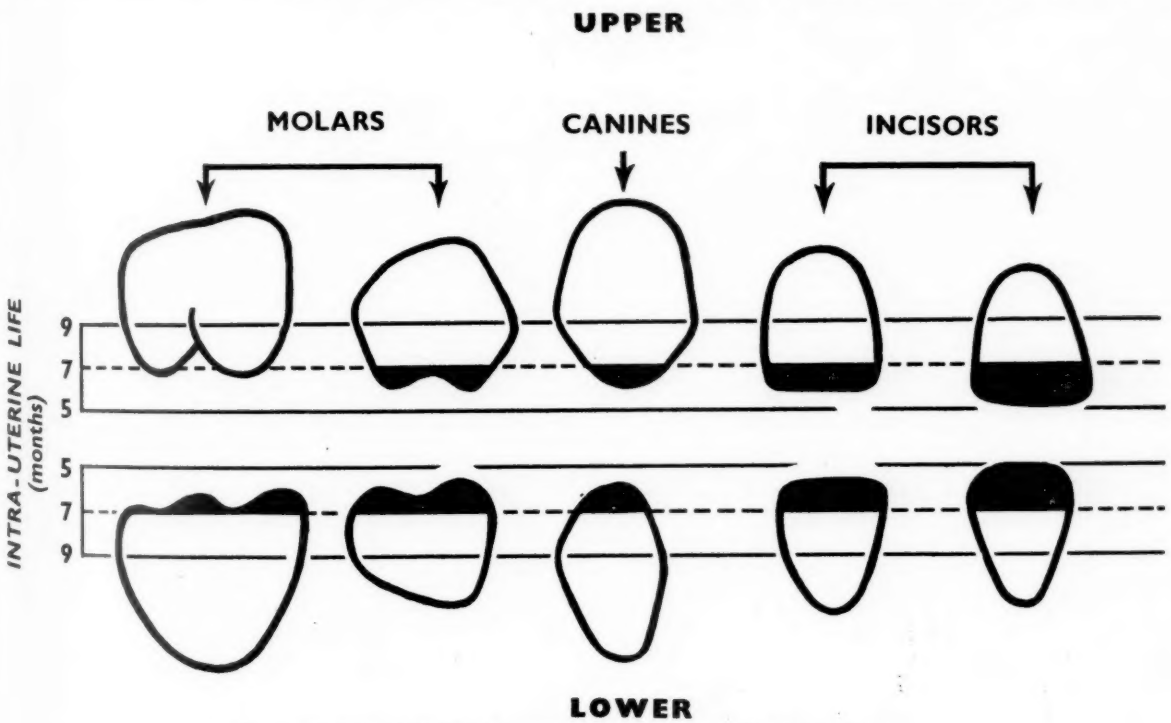

FIG. 1.—The intra-uterine development of the crowns of the deciduous teeth.

age of 6 months it was clear that P.H. had a severe cerebral palsy. Now, at the age of 3 years, he is unable to sit up. He has no speech and the lower limbs are spastic. He presents the clinical picture of severe kernikterus. The teeth show 'severe' enamel hypoplasia.

The other twin, also a boy, had a birth weight of 6 lb. 10 oz. and the Coombs test was positive. The haemoglobin of the peripheral blood shortly after birth was 96%; jaundice was apparent within the first 12 hours of life. The jaundice in this child was never as deep as in his twin, but he rapidly became anaemic. No exchange transfusion was done, but several simple transfusions were given. Apart from the anaemia this child's neonatal progress was satisfactory and there was never any clinical suggestion of kernikterus. He is now, at the age of 3 years, a normal healthy child. His teeth show neither pigmentation nor enamel hypoplasia.

Case 2 (T.L.). This child, a boy, was the sixth of normal parents. His mother was Rh negative with strong antibodies. His birth weight was 9 lb. and he developed severe and prolonged neonatal jaundice. He was born at home, and no treatment was given. His case in fact only came to light when his younger sister (D.L.) presented with retarded neuromuscular development. T.L. himself was also retarded in neuromuscular development, and now at the age of 7 years he is unsteady on his legs and has definite athetotic movements of his hands. He has a marked speech defect, associated with a severe high-tone deafness. (This aspect of his case has already been described in detail by Cavanagh (1954) who refers to him as 'Trevor L.')

His canine teeth show the 'ring' type of enamel lesion (Fig. 2). His sister D.L. is a typical, but more severe, case of kernikterus and has similar dental lesions.

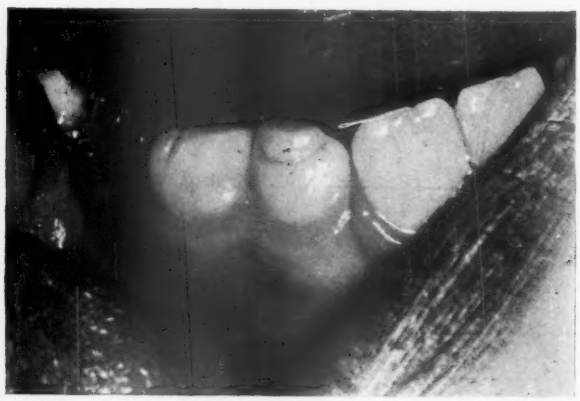

FIG. 2.—The right lower deciduous teeth of Case 2 (T.L.). The canine shows the typical 'ring' type of enamel hypoplasia.

Case 3 (P.S.). This infant, a boy, was the second child of healthy parents. The first child is alive and well. His mother was Rh negative with antibodies. His birth weight was 7 lb. The Coombs test was positive but the cord haemoglobin was 114% and it was thought that he did not need exchange transfusion. He became deeply jaundiced, however, and on the third day of life he had marked neck retraction. He appeared to have recovered when he left hospital on the 21st day. At the age of 3½ months he presented with the first of a series of hyperpyrexial attacks which recurred frequently until the time of his death at 8 months. The attacks followed the characteristic pattern described in severe forms of kernickterus (Patterson and Forrester, 1953). At the time of his death the lower central incisors had just erupted.

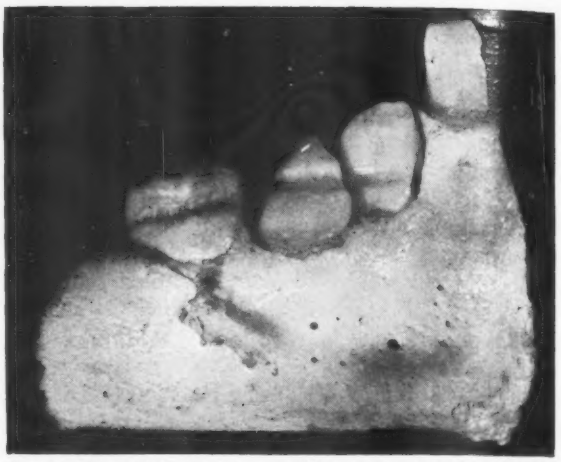

FIG. 3.—The right half of the mandible of Case 3 (P.S.). The bone has been partly removed and the teeth left *in situ*. The groove of enamel hypoplasia is most marked on the canine.

Post-mortem *x*-ray examination of the jaw showed a definite break in the continuity of the enamel outline of the canines. Dissection revealed a 'severe' enamel hypoplasia in the form of a deep groove across the lateral incisors, canines and first molars (Fig. 3).

Case 4 (B.B.). This boy was the sixth child of healthy parents. The previous children were normal. His mother was Rh positive. The child was born at home (birth weight 9 lb.) but as he developed severe jaundice he was admitted to hospital.

Apart from the jaundice no clinical evidence of haemolytic disease was discovered. There was no report of any neurological abnormality in the neonatal period. He presented at the age of 4 years with retarded neuromuscular development. He had not walked alone until well over the age of 2 years. When examined at the age of 5 years he was still ataxic and clumsy, and his hands showed athetotic movements. His speech was poorly developed and there was clinical evidence of deafness. (He was the only member of the family unable to hear the high-pitched bell of the ice-cream man.) Audiometry confirmed bilateral high-tone deafness.

The possibility of other blood group incompatibility was explored; specimens were taken from B.B. and from both parents. The report was as follows:

The mother was group OR_1R_1(CCDee), the father

A_1R_2(ccDE) and the child, group $A_1R_1R_2$(CcDEe). The anti-A in the mother's serum showed immune characteristics. No other abnormal antibodies were detected in the mother's serum.

Although ABO incompatibility may cause some difficulty in diagnosis it is now generally accepted as a cause of haemolytic disease and of kernikterus (Grumbach and Gasser, 1948; Boorman, Dodd and Trinick, 1949; Mitchell, Moss, Redner, Levy and Greenblatt, 1949; Reepmaker and van Loghem, 1953). This child (B.B.) appeared to satisfy both the clinical and serological criteria for the condition. His canine teeth showed the 'notch' form of enamel hypoplasia.

It is interesting to note that the next (seventh) infant in this family also developed severe and prolonged neonatal jaundice, but the teeth and the central nervous system are normal. The latest (eighth) infant was born in hospital and kept under close supervision. Jaundice appeared within the first 12 hours of life and at 48 hours the serum bilirubin was 19·2 mg. %. Exchange transfusion was then undertaken and the subsequent progress has been satisfactory.

Group II : Kernikterus in Premature Infants

Under this heading nine children with cerebral palsy and enamel hypoplasia are described. All were premature infants and it seems probable that in each case the diagnosis was kernikterus of prematurity. As in the cases following haemolytic disease there was variation in the site and severity of the enamel lesion, and also modification by caries and attrition. The lesions were generally most severe on the incisors but the canines and the molars were often similarly affected. It was common for the incisal third of the incisor teeth to appear free of enamel; affected canines or molars, when seen soon after eruption, showed the tips of the cusps as small sharp spikes (Fig. 4). Attrition rapidly obscured this picture but there was always the story from the parents that the teeth 'came through bad' or that they appeared 'like little needles'.

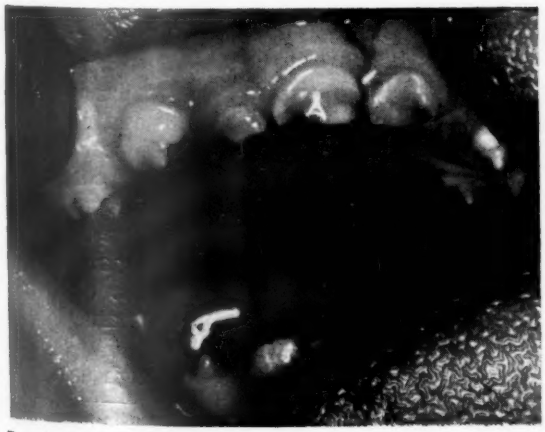

FIG. 4.—Widespread enamel hypoplasia in Case 19 (J.S.). The incisors are almost devoid of enamel; the canines and molars show spiky projections of the cusps.

The details of these cases are set out in Table 1.

Amongst these cases there are two which merit further description.

Case 17 (B.M.). The patient was one of binovular twins. The other twin (birth weight 3 lb. 9 oz.) has developed normally, without evidence of cerebral palsy or of enamel hypoplasia.

Case 18 (L.S.). The cerebral palsy in this child, a girl, is in the form of a spastic diplegia and the clinical picture closely resembles that described by Ingram and Kerr (1954) as being frequently associated with retrolental fibroplasia. Her teeth (Fig. 5) are the only ones in the whole series which show a crescent-shaped erosion (Koupernik and Buhot, 1952).

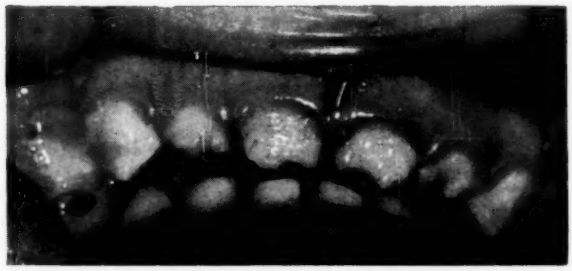

FIG. 5.—The crescent-shaped erosion of the incisor teeth in Case 18 (L.S.).

In the present state of knowledge it seems necessary to exercise some caution in making the diagnosis of kernikterus of prematurity. It is clear, however, that this condition is being recognized with increasing frequency. From a pathological viewpoint accounts have been given by Aidin, Corner and Tovey (1950), Zuelzer and Mudgett (1950), Govan and Scott (1953), and Black-Schaffer, Kambe, Furuta and Moloney (1954). The later neurological sequelae have been accepted by Koupernik and Buhot (1952), Gerrard (1952) and Sacrez, Fruhling and Heumann (1952). These authors are agreed that the sequelae are indistinguishable whether they originate in prematurity or haemolytic disease.

The diagnosis in each individual case described must be the subject of opinion but there appears to be so much in common between our Group II cases that their description as a group is justified, and their very existence lends support to the concept

TABLE 1
CLINICAL DETAILS OF GROUP II

Case	Birth Weight (lb. oz.)	Exposure to Raised Oxygen Concentration (Days)	Neonatal History	Present State
14 (PD)	3–5	16	No unusual incidents recorded; no record of jaundice. Early changes of retrolental fibroplasia, but eyes now normal.	Cerebral palsy with spastic legs a.. bilateral internal strabismus. She cannot sit unaided at the age of 2 years.
15 (VG)	2–8	44	Frequent cyanotic attacks between 15th and 21st day of life. No record of jaundice. Early changes of retrolental fibroplasia, but eyes now normal.	Cerebral palsy of hypotonic type. She is beginning to walk alone at the age of 3 years.
16 (A.J.)	4–0	12	General condition and progress normal apart from marked jaundice which lasted from the 3rd to the 13th day of life. Early changes of retrolental fibroplasia were noted on the 22nd day.	Cerebral palsy with mildly spastic legs and hypotonic trunk muscles. Left eye normal; right eye incomplete retrolental membrane.
17 (B.M.)	2–5	14	Normal development. The eyes were examined regularly. No evidence of retrolental fibroplasia.	Mild cerebral palsy with delayed walking. She did not sit alone until the age of 1 year and at 2½ years she has a wide-based, unsteady gait, and bilateral internal strabismus.
18 (L.S.)	2–15	54	Uneventful except for severe jaundice which had cleared by the 16th day. Fundi not examined in the neonatal period.	Blind; complete bilateral retrolental membranes. Cerebral diplegia; she is beginning to stand with both hands held at the age of 3 years.
19 (J.S.)	3–3	36	Cyanotic attacks on the 6th day only; no record of jaundice. Mild early changes of retrolental fibroplasia, but now normal.	Athetoid type of cerebral palsy. Clinical evidence of deafness. He is beginning to stand with hands held at age of 2 years.
20 (B.W.)	4–0	?	Intermittent cyanotic attacks up to age of 21 days; jaundice of unspecified duration; fundi not examined; no record of oxygen administration.	Cerebral palsy with delayed walking and speech. He first sat alone at the age of 15 months; now at the age of 6 years he walks almost normally, but shows considerable incoordination when attempting to run. There is clinical evidence of high tone deafness. His eyes are normal.
21 (S.K.)	2–9	41	Jaundice recorded as slight from the 2nd to the 8th day; nothing otherwise abnormal. The eyes were not examined in the neonatal period.	Blind; complete bilateral retrolental membranes. Cerebral palsy of hypotonic type with delayed sitting and walking. He is just walking with hands held at the age of 3½ years.
22 (S.R.)	4–6	(1 hour)	Mild jaundice noted on the 4th day, otherwise nothing abnormal. Eyes examined regularly; no evidence of retrolental fibroplasia.	Mild cerebral palsy. He did not sit alone until the age of 15 months. At 20 months he is beginning to pull himself to standing and to use his hands to feed himself.

of a common basic pathological process in all forms of kernikterus.

A history of neonatal jaundice has sometimes been lacking in the Group II cases. This is not unexpected, for they were observed by many different individuals and under different conditions of lighting. There will be marked differences between observers in describing the depth of jaundice observed in any one case, and the colour of the skin is a very inaccurate measure of the serum bilirubin (Davidson, Merritt and Weech, 1941). Often jaundice, although observed, goes unrecorded in the premature infant as it is so common and so widely regarded as physiological.

The relationship between ABO incompatibility and kernikterus of prematurity has been much discussed. Gerrard (1950) found no such relationship, but Levine, Vogel and Rosenfield (1953) suggest that such incompatibility may play at least a part in this condition. All the cases in Group I were subjected to a full serological examination. The results are set out in Table 2. It will be noted that there are only five cases in which incompatibility can be excluded as a contributory factor (Nos. 14, 17, 20, 21, 22) ; in no case, however, had there been obvious evidence of haemolytic disease in the neonatal period.*

The Incidence of Enamel Hypoplasia in Other Conditions

There are few studies on enamel hypoplasia in deciduous teeth. Mellanby and Mellanby (1950) report the incidence of 'gross hypoplasia' in normal children as 0·7% and those cases appear to have shown changes which would generally correspond to the lesions described in this paper as 'mild'. No lesions comparable to a 'severe' type were described. Amongst 136 rachitic children, Shelling and Anderson (1936) reported an 18% incidence of enamel hypoplasia, but did not describe the nature of the lesions.

Hess and Abramson (1931), although unable to

* The serology in these cases was carried out at the National Blood Transfusion Laboratories, Manchester, by Dr. P. H. Renton and Dr. F. Stratton and may be the subject of a more detailed report at a later date.

TABLE 2
SEROLOGICAL INVESTIGATION OF GROUP II CASES

Case	Mother	Child	Remarks
14 (P.D.)	A.R_1R_1(CCDee)	A.R_1r(CcDee)	No incompatibility detected between child's cells and maternal serum.
15 (V.G.)	O.R_2(ccDE)	A.R_2(ccDE)	No abnormal antibodies detected in maternal serum, but doubtful evidence of immune anti-A.
16 (A.J.)	A.R_1R_2(CcDE)	AB.R_1(CDee)	Mother's serum showed doubtful evidence of an immune anti-B; a weak anti-M, active only in the cold, was also present.
17 (B.M.)	A.r.r(ccddee)	A.R_1r(CcDee)	No incompatibility detected between child's cells and maternal serum.
18 (L.S.)	O.R_1r(CcDee)	B.R_1(CDee)	No abnormal antibodies detected in maternal serum, but her anti-B showed immune characteristics.
19 (J.S.)	B.R_1R_1(CCDee)	ABR$_1$r(CcDee)	No abnormal antibodies detected in maternal serum; her anti-A did not show immune characteristics.
20 (B.W.)	O.rr(ccddee)	O.rr(ccddee)	No incompatibility detected between maternal serum and child's cells.
21 (S.K.)	A.rr(ccddee)	A.R_1r.(CcDee)	No incompatibility detected between maternal serum and child's cells.
22 (S.R.)	O.R_1r(CcDee)	O.R_1R_1(CCDee)	No incompatibility detected between maternal serum and child's cells.

associate enamel hypoplasia with any one disease, noted that amongst their cases 'the number of premature children was inordinately high.' Stein (1947) observed severe enamel hypoplasia involving the incisal third of the incisors in eight out of 16 premature infants.

Schour and Kronfeld (1938) record one further example of enamel hypoplasia which was as severe as that reported in this paper. Their patient appears to have suffered from cerebral palsy, and it is interesting to note in retrospect that the history and post-mortem findings are entirely consistent with a diagnosis of kernikterus.

The existence of enamel hypoplasia in a sporadic form made it necessary to examine our own cases critically and to make sure that the dental lesions were not associated with some underlying pathological cause other than kernikterus. It was obvious that in Group I, haemolytic disease itself, rather than kernikterus, was a selecting factor. In Group II retrolental fibroplasia and prematurity were selecting factors. In both groups cerebral palsy of varying degree was present and could have exercised a similar selecting influence. It was necessary, therefore, to study the incidence of enamel hypoplasia in these and other conditions, when not associated with kernikterus.

Normal Children. One hundred and nine toddlers were examined. All these children were making routine attendances at an infant welfare clinic; all were reported to be well. 'Mild' hypoplasia was found in four cases, but on looking into their histories it was noted that three had been premature infants with birth weights close to 5 lb. The fourth was the child of a mother who had syphilis; this condition was discovered and treated during the pregnancy and the child was otherwise normal. No other examples of hypoplasia were found in this group of children.

Haemolytic Disease. Forty-five children were examined. Each satisfied the criteria of Rh incompatibility: a positive Coombs test and clinical evidence of haemolytic disease. All except one were full-term infants. Thirteen had had exchange transfusions. 'Mild' enamel hypoplasia was discovered in nine cases and green teeth in seven. No examples of 'severe' hypoplasia were found. None of these children showed any neurological disturbance.

TABLE 3
INCIDENCE OF SEVERE ENAMEL HYPOPLASIA IN CONTROL GROUPS

Group	Total Cases Examined	Severe Enamel Hypoplasia	
		Total	% Incidence
Normal children	109 less 4 cases (3 premature and one maternal syphilis) = 105	0	0
Haemolytic disease without kernikterus	45	0	0
Premature infants with retrolental fibroplasia (average birth weight 3 lb.)	65 less 3 with kernikterus = 62	9	9/62 = 16%
Unselected premature infants	34	7	7/34 = 20%
Cerebral palsy (other than kernikterus)	11	0	0

Enamel hypoplasia and pigmentation were found together in only one case.

Premature Infants. Ninety-nine infants were examined. They were drawn from two separate sources.

A first group of 65 were examined in the Sunshine Homes of the Royal National Institute for the Blind; all had been blinded by retrolental fibroplasia; their birth weights ranged from 2½ to 4½ lb. (average 3 lb.). 'Severe' enamel hypoplasia was found in 12 cases, being most marked in three children who also showed definite evidence of retarded neuromuscular development. Both dentally and neurologically these three were indistinguishable from the children described in Group II as examples of kernikterus. The enamel lesions in the other nine cases were similar to those described below as occurring in normal premature infants.

Thirty-four premature infants were seen in a routine follow-up clinic. Their birth weights ranged from 2 lb. 5 oz. to 4 lb. 10 oz. (average 3 lb. 10 oz.). 'Severe' enamel hypoplasia was found in seven cases. In all seven, however, it was limited to the upper central incisors, and affected only one or two millimetres of the incisal edge of the tooth. In none of these cases was there any evidence of cerebral palsy.

Cerebral Palsy. Twelve children with cerebral palsy were examined. All were between the ages of 3 and 5 years and were making routine attendances at out-patient clinics. Eleven had normal teeth; the twelfth had 'severe' enamel hypoplasia; on going into her history it was found that she had been a premature infant with a birth weight of 3 lb. 13 oz. and that she had had severe neonatal jaundice. She had an ataxic form of cerebral palsy and was known to have partial bilateral nerve deafness. She was regarded, on clinical grounds, as a further case of kernikterus of prematurity.

It is now possible to compare the incidence of 'severe' enamel hypoplasia in these control groups (Table 3). In each group the cases regarded as further examples of kernikterus have been excluded from the calculation of incidence. The low incidence of hypoplasia in normal children is in accordance with Mellanby's findings. The comparatively high incidence in premature infants agrees with the findings of Stein and of Hess and Abramson.

It is emphasized, however, that although 'severe' hypoplasia was observed in normal premature infants it was almost entirely confined to the upper central incisors, whereas when associated with cerebral palsy the lesion was widespread throughout the deciduous dentition.

Discussion

It has already been noted that the site of hypoplasia on a tooth is related to the age at which metabolism was disturbed. This concept fits closely with our own findings. Thus in the premature infants (Group II) the incisors have always been severely involved; the canines and molars have usually been affected at the cusp tip. In the cases of full-term infants (Group I) the incisors have often been normal, and the lesions on the canines and molars have been nearer the gum margin.

It has been interesting to note the absence of green pigmentation in the cases with 'severe' hypoplasia. Pigmentation, when it does occur, is most evident in the dentine (Miller, 1951; Marsland and Gerrard, 1953). The absence of the pigment in the cases now reported suggests that the disturbance responsible for the enamel lesion may also have been severe enough to arrest development of the dentine. Preliminary investigation of material from these cases supports this hypothesis, and also suggests that the neonatal lines' which can be seen in 'normal' enamel may be associated with 'physiological' neonatal jaundice.

The relationship between enamel hypoplasia and bilirubin itself requires further study; work on this and on related matters is in progress and will be reported in detail at a later date. It seems certain from the occurrence of these enamel lesions that severe metabolic disturbance is associated with both severe haemolytic disease and premature birth. It seems that in both types the disturbance occurs in the first few days of extrauterine life.

Microscopically the enamel which is formed pre-natally can be distinguished from that which is formed post-natally by the neonatal line of Rushton (1933). It was observed in the 'severe' hypoplastic areas that there was prenatal enamel but no post-natal enamel. This indicates that the lesions resulted from a metabolic disturbance shortly after birth and offers further evidence in support of the view that kernikterus is a post-natal phenomenon.

The similarity between the pathological and the neurological changes recognized in all forms of kernikterus has suggested a common underlying factor, which Govan and Scott (1953) thought might be anoxia. Other writers have tended to incriminate bilirubin. Black-Schaffer *et al.* (1954) have recently summarized these views. Which, if either, of these two possible causes is related to the enamel lesion is a matter for conjecture and experiment. It seems probable, however, that the elucidation of the dental problem may throw some light on the aetiology of kernikterus itself.

Apart from the significance of these changes from

the dental and pathological viewpoint, their presence in any individual can be of direct help in clinical practice. The discovery of typical changes in any case of cerebral palsy will suggest a diagnosis of kernikterus, and this in turn will lead to the suspicion that partial deafness may complicate the child's disability. The presence of kernikterus may be anticipated by the discovery of typical *x*-ray changes before any teeth have erupted and before retarded neuromuscular development has become apparent.

From an otologist's viewpoint the presence of these lesions in any case of congenital deafness should lead at once to enquiry into the possibility of kernikterus.

Summary

In 13 cases of kernikterus following haemolytic disease an acute enamel hypoplasia of the deciduous teeth was observed. Similar lesions were found in nine premature infants who had developed cerebral palsy; these cases are tentatively cited as examples of 'kernikterus of prematurity'.

Similar but milder enamel lesions have been found in normal premature infants but not in full-term children in the absence of kernikterus.

The cause of the enamel lesion is not established but it is suggested that the elucidation of this problem may throw some light on the cause of the damage to the central nervous system. Attention is drawn to the diagnostic value of these changes in cases of cerebral palsy or congenital deafness.

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Dr. C. E. Potter and Mr. M. Colborne Brown kindly permitted us to examine the children in the Sunshine Homes; we are indebted to the headmistresses and staff of the Sunshine Homes at Southport, Kingswinsford, Leamington and Northwood for their help.

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ON A SEARCH FOR RHESUS ANTIBODIES IN VERY YOUNG FOETUSES

BY

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The first Rh-sensitized pregnancies of Rh-negative women do not end in death of the embryo or foetus more often than do the pregnancies of other women. In subsequent sensitized pregnancies the death rate of Rh-positive foetuses is markedly increased. These latter foetal deaths always occur in the second half, and most of them in the last third, of pregnancy: Rh-sensitization is not a cause of death of the embryo or of the foetus under about 20 weeks. The reason for this is unknown, but it has been suggested that the maternal antibodies do not reach the embryo or the foetus in the early weeks of gestation. I have recently had the opportunity of examining a young foetus from each of two sensitized Rh-negative women: the following are my observations on them.

Case 1

The husband was AB, CDe cDE, the wife A, cde cde. The woman had had anti-Rh antibodies since the time of her first pregnancy in 1946; at the time of the expulsion of the foetus to be discussed the titre was 2 in albumin, a trace in saline. The foetus was the product of her fourth pregnancy and was aborted spontaneously at about 10 weeks in March, 1954: the placenta and membranes were missing.

The foetus measured 59 mm. in crown-rump length, weighed 9·8 g. and appeared normal externally. There was no maceration. Blood was obtained from the cord and from the heart, and was in good condition. The red cells were Group A, Rh-positive (CDe cde), direct-Coombs negative, but strongly indirect-Coombs positive with incomplete anti-D. We have observed that the fluid from the various body cavities and from the skin blebs of stillborn foetuses contain Rh antibodies if the blood contains them. Two drops of clear, pale yellow fluid were obtained from each pleural cavity of the present foetus. This fluid did not agglutinate Rh-positive red cells by the saline, albumin or indirect Coombs method. The foetal tissues, now largely drained of blood, were homogenized in a waring blender with double their weight of saline. The filtrate did not agglutinate Rh-positive red cells by any method.

The maternal antibody could not be shown to be present in the foetus, but this is not surprising since the antibody had a titre of only 2. The red cells of the foetus were capable of absorbing both complete and incomplete Rh antibody. The abortion is not to be ascribed to Rh sensitization.

Case 2

The woman was O, cde cde. Rh antibodies had been present since 1947 during her fourth pregnancy; at the time of the removal of the foetus to be discussed the titre was 64 in albumin, 1 in saline. The foetus was the product of her eleventh pregnancy for eight of which, including this one, her husband was not the father. He is Rh-negative (O, cde cde). Hysterectomy was carried out at six weeks in December, 1954, on the recommendation of a consulting psychiatrist.

I received the intact ovum direct from the operating room. Taking care not to manipulate the placenta I made a small incision into the amniotic sac, introduced a large-bore needle attached to a syringe and tried to aspirate the fluid. I could obtain only a drop or two of fluid at a time, the needle then becoming obstructed by transparent filaments I could not see. This fluid was palely yellow. After repeated failure to obtain fluid in quantity in this way I opened the sac more widely, placed the tip of the needle in its most dependent point and readily withdrew 5 ml. of water-clear, colourless fluid. My impression was that there were two compartments in the sac, one possibly loculated and containing pale yellow fluid, the other fully open and containing colourless fluid. Whether the pigment in the first fluid had any pathological significance I cannot say: it was not examined for bile pigments. I now clamped the cord at both ends and removed the foetus and cord from the sac.

The crown-rump length of the foetus was 32 mm.; its weight, 2·59 g. The cord blood was A, cDE cde, direct-Coombs positive. I opened the body, obtained two or three drops of blood with a Pasteur pipette, spun this down, recovered a small drop of serum, diluted this with an equal quantity of saline and set the mixture up with group A, Rh-positive and group A, Rh-negative cells in parallel for an indirect Coombs test. The

Rh-positive cells were strongly agglutinated; the Rh-negative cells were not agglutinated. There was no serum left to carry titration farther.

The maternal antibody had already reached the foetal circulation at this early age: part was attached to the red cells, part free in the plasma. The presence of the antibody in the foetal circulation was not the result of the surgical manipulation of the uterus or the ovum, for, had it been, maternal anti-A as well as anti-D would have been present. No anti-A was demonstrable. No conclusion can be reached about the significance of the pigment in the amniotic fluid.

Summary

Two Rh-positive foetuses of sensitized Rh-negative women were examined. In the first case the mother had an anti-Rh albumin antibody with a titre of 2. The foetus was about 10 weeks old. No antibody could be demonstrated in its blood or tissue fluids. In the second case the mother had a titre of 64; the foetal cells were direct-Coombs positive; the serum contained anti-Rh albumin antibody. A portion of the amniotic fluid of the latter foetus was palely yellow.

I am grateful to Drs. A. M. Goodwin, M. Brookler and A. I. Lerner for their kindness in obtaining the foetuses for me.

OBSTRUCTIVE JAUNDICE IN HAEMOLYTIC DISEASE OF THE NEWBORN TREATED WITH MAGNESIUM SULPHATE

BY

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Obstructive jaundice seldom follows haemolytic disease of the newborn. It may occur at the height of the haemolytic process or not until some weeks later. In the latter instance, an evanescent phase of haemolytic jaundice may occur after birth with a recurrence of icterus after a few weeks, and then biliary obstruction. The degree of biliary obstruction is usually only partial but it may be complete. Jaundice may continue for any period between 3 weeks and 6 months of age, with an average duration of seven to eight weeks (Hsia, Patterson, Allen, Diamond and Gellis, 1952).

Still (1927) was the first to describe this type of obstructive jaundice and he thought that the bile arising from excessive haemolysis had become too viscid to pass freely along the ducts. Ladd (1935) also considered that some of these cases of obstructive jaundice were due to 'inspissated bile', with stenosis or narrowing of the common duct though without definite evidence of atresia. Skelton and Tovey (1945) accepted the inspissated bile theory but also suggested that, in some cases, the bile ducts might be converted into a fibrous cord following organization of a plug of inspissated bile. Lightwood and Bodian (1946) thought that the inspissated bile theory did not adequately explain the facts and pointed out that a markedly obstructive phase did not necessarily go with the greatest haemolysis nor with the deepest preceding jaundice. They suggested that biliary obstruction was due to swelling of damaged liver cells. Gilmour (1944) and Craig (1950) have described the post-mortem appearances in the liver consisting of erythropoiesis, distortion of hepatic cords, pigmentation and necrosis of liver cells and bile thrombi in the canaliculi. Craig also noted giant multinucleated cells and suggested that they might accompany regeneration of liver cells in young infants.

Hsia *et al.* (1952), discussing both theories, thought that it was not clear whether inspissation occurred as the result of damage to the liver parenchyma or whether the excessive load of bilirubin presented to the liver caused blockage of the ducts during excretion. Assuming the latter to be true, it was probable that the biliary system was gradually cleared of inspissated bile as the haemolytic process ceased and as the bile ducts became larger. The fact that obstructive jaundice occurs in some patients and not in others might, they thought, be due to variation in functional maturity of the liver and size of the bile ducts in infants. Harris, Andersen and Day (1954) agreed with Bodian and Lightwood that the major abnormality was in the liver cells and that plugs of inspissated bile in the biliary canaliculi were present as a secondary phenomenon. This also occurs in infective hepatitis where stagnation of bile may be seen in canaliculi just outside the areas of maximal necrosis.

Two cases of obstructive jaundice associated with haemolytic disease of the newborn will now be reported and their treatment described.

Case Reports

Case 1. This girl was born in hospital and weighed 6 lb. 11 oz. at birth. The mother was Rh negative and her one previous baby had not been affected by haemolytic disease. This second baby was jaundiced at birth, the direct Coombs test on the cord blood was positive, and an exchange transfusion (350 ml.) was given soon after birth. All jaundice had disappeared at the age of 2 weeks and the baby's stools were then normal in colour. A further blood transfusion (100 ml.) was given at that time as she was anaemic. At the age of 26 days the baby suddenly became jaundiced once more and her stools were noticed to be very pale. She was admitted to hospital at the age of 28 days and was then deeply jaundiced; the liver and spleen were enlarged, the urine was dark and the stools were very pale.

Investigations gave the following results:

Haemoglobin, 50% (7·4 g. %); white cell count, 6,000 per c.mm. (2 late normoblasts per 100 nucleated cells); reticulocyte count, 2·8 %; red cell fragility test, normal; blood Wassermann reaction, negative; blood group, O Rh positive. The urine contained bile pigments; otherwise it was normal. Fouchet's test for faecal bilirubin was negative.

Liver function tests gave serum bilirubin, 8·0 mg. %, serum alkaline phosphatase, 13 units % (King-Armstrong); thymol flocculation, negative; thymol turbidity, 0·8 units.

Two days after admission the serum bilirubin had risen to 14·4 mg. % and the haemoglobin had fallen to 46% (6·8 g. %). Duodenal intubation was carried out on the seventh hospital day and 10 grains of magnesium sulphate (2·6 ml. of a 25% solution) were given into the duodenum. On the same evening the baby passed a bile-stained stool and a similar stool was passed on the following day. Duodenal intubation was repeated on the ninth hospital day and the same dose of magnesium sulphate was administered. Two days later the stools contained the normal amount of bile pigment and the serum bilirubin had fallen to 4 mg. %. By this time the baby's jaundice was fading rapidly and she had begun to gain weight for the first time since admission. Duodenal intubation was repeated on the twelfth hospital day and a further dose of magnesium sulphate was given. A blood transfusion was then given to correct the anaemia and she was discharged after 15 days in hospital. She was seen as an out-patient three weeks later, when her general condition was satisfactory. She had gained weight, the stools were normal in colour, and the liver and spleen were just palpable. Haemoglobin was 87% (12·8 g. %), serum bilirubin was 0·5 % and serum alkaline phosphatase was 16 K.-A. units %. Her subsequent progress was uneventful.

Case 2. This girl was born in hospital at term and weighed 6 lb. 13 oz. at birth. The mother, who was Rh-negative, had had 13 pregnancies. Four of her babies had been stillborn but there was no record of their having been affected by haemolytic disease. Only one previous child, the eleventh in birth rank, had been jaundiced at birth. He received a blood transfusion in the neonatal period and his subsequent growth and development were normal. The mother had not had any miscarriages, blood transfusions or injections of blood or plasma, and she had never suffered from jaundice herself. Her serum had been examined for Rh antibodies in the fifth month of the present pregnancy but none were found.

At birth, the child was covered with golden yellow vernix but there was no jaundice and the liver and spleen were not enlarged. The cord blood haemoglobin was 97% (14·4 g. %) and the direct Coombs test on the cord blood was negative. A tinge of jaundice was noted on the second day of life; the peripheral blood haemoglobin was then 97% (14·4 g. %). All trace of jaundice had disappeared by the fourth day, when the direct Coombs test was repeated and was still negative. The baby was removed from hospital against medical advice on that day.

She remained well until the age of 6 weeks, when jaundice reappeared. The baby was still jaundiced when seen in hospital at the age of 9 weeks and dark urine and pale stools had been noted by the mother during the preceding week. She weighed 8 lb. 8 oz. and the liver and spleen were enlarged, the liver edge being felt 3 cm. below the right costal margin in the nipple line.

Investigations gave the following results:

Haemoglobin, 70% (10·4 g. %); white cell count, 10,000 per c.mm. (2 late normoblasts per 100 nucleated cells); reticulocyte count, 2·8%; blood Wassermann reaction, negative; blood group, O Rh-positive.

The urine contained bile pigments, otherwise it was normal. The faeces were grey in colour, and Fouchet's test for bilirubin was negative.

Liver function tests gave serum bilirubin, 5·2 mg. %; serum alkaline phosphatase, 29 (King-Armstrong) units %; thymol flocculation negative; and thymol turbidity, 0·6 units.

Rhesus antibodies were demonstrated in the mother's serum in albumin and saline, and the indirect Coombs test, using the baby's red cells and the mother's serum, was strongly positive. The direct Coombs test was negative.

The first duodenal intubation was performed on the tenth hospital day and 10 grains of magnesium sulphate (2·6 ml. of a 25% solution) were given into the duodenum. No change in the colour of the stools occurred and, two days later, the serum bilirubin was 5·4 mg. % and the serum alkaline phosphatase was 47 units %. Duodenal intubation was repeated on the thirteenth hospital day and 20 grains of magnesium sulphate (5·2 ml. of a 25% solution) were given. After this, the baby's stools were faintly coloured and Fouchet's test became positive for the first time. The stools continued to be green-stained over the next few days and the serum bilirubin fell to 3·35 mg. %. Duodenal intubation was repeated on the twentieth hospital day and 40 grains of magnesium sulphate (5·2 ml. of a 50% solution) were given. Following this, she had severe diarrhoea for 24 hours. Over the next week she continued to pass faintly bile-stained stools and her serum bilirubin fell to 2·8 mg. %. Nine days after the last duodenal intubation, she began to pass dark, bile-stained stools and the jaundice disappeared over the next 48 hours; the serum bilirubin level fell sharply to 0·9 mg. % at this time. Following the disappearance of jaundice, she began to gain weight for the first time since admission, and the liver, which had been enlarged to a point 4·5 cm. below the right costal margin, returned to its normal size over the next two weeks. She was discharged in a satisfactory condition after eight weeks in hospital, and when she was seen as an out-patient five weeks later she had gained 4 lb. in weight, the stools were normal in colour and the liver and spleen were just palpable. Haemoglobin was 68% (10·1 g. %), serum bilirubin was less than 0·5 mg. % and serum alkaline phosphatase was 20 units %. Her subsequent progress was uneventful.

Discussion

In general, authors agree that the prognosis of obstructive jaundice following haemolytic disease of the newborn is good but when the jaundice is prolonged cirrhosis may follow (Lightwood and Bodian, 1946). It is not clear whether this cirrhosis develops as a result of prolonged biliary obstruction or whether it should be ascribed to a severe degree of hepatitis. If it is due to obstruction of the biliary passages there would seem to be a case for promoting the flow of bile if possible. This may be attempted by medical or surgical means but the risks of surgical intervention in infants under the age of 3 months with liver damage are well known (Janeway, 1951; Hsia *et al.*, 1952; Harris *et al.*, 1954). Patterson (1952) used 20% sodium dehydrocholate intravenously and bile salts orally in 10 infants with this condition, and he reported an increased flow of bile following the use of these cholagogues: biliary flow was resumed in three cases immediately; five cases had a normal biliary flow after seven days, and flow was resumed in the remaining two cases after 14 and 21 days respectively.

In the two cases described in this paper, magnesium sulphate in a concentrated solution was chosen as the cholagogue. When magnesium sulphate is introduced into the duodenum it causes evacuation of the gall-bladder and relaxation of the sphincter of Oddi. Lyon (1929) demonstrated this action by cholecystography and recommended the use of intraduodenal magnesium sulphate in various disorders of the liver and blood.

In the first of the two cases described, the association between the administration of intraduodenal magnesium sulphate and the relief of the jaundice seemed to be very striking. Within six hours of the first duodenal intubation the baby began to pass bile-stained stools and, following the second intubation, the stools became heavily bile-stained and the jaundice rapidly disappeared. In the second case, the association between the administration of the drug and the relief of the jaundice was not so clear cut. However, following the second intubation, the baby's stools became bile-stained and the serum bilirubin fell by 2 mg. % over the next few days. Further slight improvement followed the third intubation but the jaundice did not finally clear until nine days after the last intubation. In this case, relief of the jaundice might have taken place at this time without any treatment but it seems reasonable to suppose that the administration of intraduodenal magnesium sulphate may have helped to dislodge some of the 'inspissated' bile and so have led to the disappearance of the jaundice.

Finally, it should be mentioned that duodenal intubation is sometimes a rather time-consuming procedure in young infants. However, the results of the administration of magnesium sulphate by this method in these two cases would seem to justify a further trial.

Summary

Theories relating to the pathogenesis of obstructive jaundice following haemolytic disease of the newborn are discussed.

The clinical features of two infants with this condition and their treatment with intraduodenal magnesium sulphate are described.

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NUCLEAR AGENESIS

MÖBIUS' SYNDROME: THE CONGENITAL FACIAL DIPLEGIA SYNDROME

BY

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'The immobility of this man's face is very striking; it is as smooth and expressionless as if carved out of wood. The passions and emotions of eighteen years have left no trace upon it, and time has changed only its size.'

Thus Harlan (1881) described the appearance of a patient with bilateral congenital facial and external rectus paralysis. Chisholm's account (1882) was equally clear. The collation of cases of congenital facial palsy combined with other cranial muscle weakness by Möbius (1892) led to more general recognition of nuclear degeneration (as he termed it), or agenesis, and to eponymous fame.

More recently Henderson (1939) and Danis (1945) have fully reviewed the condition. Paralysis may be total or partial, unilateral or bilateral. The face is practically always involved, the external rectus muscles rather commonly, those supplied by the twelfth, third and fifth nerves, and the palate, may be affected. The weakness or paralysis is assumed to be due to aplasia of the appropriate nuclei, but the pathological evidence is hard to interpret, and until it becomes decisive, ideas about the nature of the condition must depend partly on consideration of how the various cranial paralyses come to be associated. Further weight must be attached to the circumstantial evidence provided by other congenital anomalies found in these patients. Most of them have been seen and recorded in adolescence and adult life, but patients seen in early childhood may show additional features, for example, mandibular hypoplasia and laryngeal stridor, which do not appear in other lists such as Wilson's (1940): epicanthus, absence of lacrymal caruncles, microphthalmia, deformed ears, syndactyly, micromely, localized muscle defects and club foot.

The following account includes all the cases that I have seen. Those with solitary unilateral facial paralysis are omitted, for in them the common presence of deformity of the face and external ear suggests that simple pressure by the shoulder may have produced the deformation of adjacent structures during intra-uterine life (Browne, 1936).

Case 1. Unilateral External Rectus and Facial Palsy

C.P., a boy, was born in 1948. He was the second child of healthy parents not related by blood; there was no illness during pregnancy; he was born by normal labour, at term, and weighed 6 lb. Right facial weakness was noticed at once; he could not suck well but was breast fed for two months. Because gain in weight was slow he was brought to hospital at 3 months. Weakness of the right external rectus muscle was noted. At 5 months there was slight hypoplasia of the right side of the face, which was completely paralysed. At 9 months there was a right convergent squint, which was treated operatively when he was 23 months old.

Case 2. Bilateral External Rectus and Unilateral Facial Palsy and Symbrachydactyly of the Hands

C.A., a girl, was born in 1952. She was the second child of healthy parents not related by blood; there was no illness during pregnancy; she was born at term by normal labour. She was seen at 5 months; her general condition was good but she had bilateral sixth nerve palsy; facial movements were normal on the right, but on the left the brow was always smooth, the eyelids flickered but did not meet, there was a little movement of the upper lip (a recent development not present in the earlier months), the mouth was pulled down almost normally. The hands were small and symmetrical; the fifth digit was perhaps of normal size but the others were reduced to its length, and there was syndactyly with the middle three digits fused as far as the base of the nails while the thumb and the little finger were joined to the central mass up to the level of the base of the intermediate phalanx. The feet showed slight metatarsus varus with some reduction in size of the third digit on each side.

Case 3. Unilateral Facial and Bilateral Palatal Palsy

M.D., a girl, was born in 1944. She was the third of four children of healthy parents unrelated by blood, there was no illness during pregnancy; she was born at term by normal labour. Difficulty in swallowing was noticed in the maternity hospital; until she was 5 years old solids and fluids came down the nose and even when she was nearly 9, liquids occasionally did so. In most ways she developed well but speech was unintelligible for a long time and nocturnal enuresis is still

troublesome. Speech therapy was started at 6 years.

On examination at 8 years 11 months, she was seen to be a well grown healthy American child, with no abnormalities except severe but not complete symmetrical palatal paralysis, and weakness of the left labial muscles.

Case 4. Unilateral Facial and Lingual Palsy, Micrognathia, Laryngeal Stridor and Left Talipes

C.A., a boy, was born in 1950. He was the youngest of five children of healthy parents who were not related by blood; there was no illness during pregnancy; he was born by normal labour, at term, and weighed 8 lb. Left talipes equinovarus was noticed at birth. He slept for most of the first three days, then he became more active and stridor was noticed. The tongue was seen to be abnormal at 5 days; he could not suck well, and breast feeding was early abandoned; at 10 weeks he was admitted to hospital on account of undernourishment, vomiting, choking and going blue while being fed. He had a loud, high-pitched, inspiratory stridor unaffected by the position of the head or tongue. There was weakness of the whole of the face on the left, the mandible was small, the tongue was protruded to the left and its left side was small and wrinkled and showed fibrillation. The palate was not moving when he was first seen, but a week later it was moving well; he had been fed by gastric tube and was much stronger.

Feeding was difficult throughout the first year. When he was last seen, at 14 months, he could not sit quite steadily but he appeared to be moderately intelligent and was using two words. Stridor was still audible.

Case 5. Bilateral Facial and Lingual and Possibly Masseteric and Unilateral Palatal Palsy

M.R., a boy, was born in 1942. He was the youngest of three children of healthy parents; he was born by normal labour, at term, and weighed 9½ lb. There was no stridor. He sat and walked at the expected times, but at 2 years was not speaking, so a 'tongue-tie' was cut, with no improvement. The teeth were not carious. At 4 years he was still dribbling. His intelligence was tested next year, and was within the normal range (I.Q. 85). At 6 years he was seen by Dr. W. G. Wyllie, who noted weakness of the muscles of mastication on both sides and that the tongue could not be protruded but was not wasted; the palate moved up to the left; there was slight weakness of the face on the right but it was more severe on the left. The child guided food to his teeth with his fingers. In spite of his difficulties he did well at an ordinary school. At 9 years facial movement was scanty, but the only definite weakness was in firmness when closing the left eye. The right side of the palate was paralysed and the voice was nasal as well as indistinct, the tongue being still protruded only to the teeth. There was at this time no fifth nerve weakness, mastication being difficult only because the tongue did not guide food to the teeth. Facial sensation was normal, and there was no loss of taste on the anterior two-thirds of the tongue.

Case 6. Bilateral Facial, Palatal and Masseteric Palsy, Doubtful Wasting of Tongue and Micrognathia

F.C., a boy, was born in 1948. A detailed early history was not available, but it was known that he could not suck as a baby, and had to be admitted to hospital where he was tube fed and then spoon fed. Subsequently, he was treated for malocclusion of the teeth, and the tonsils and adenoids were removed. An intelligence test, performed because he 'looked vacant', placed him in the normal range (I.Q. 104) and he was found to be cooperative in speech therapy. When he was seen at 4¼ years he was a healthy blonde boy with blue eyes. The lower jaw was small, there was bilateral facial weakness, more pronounced on the left than the right, and the masseters were weak. The tongue was small and wrinkled but was protruded fairly well. The palate moved poorly, and when the post-nasal space was examined with a nasopharyngoscope 'the soft palate was seen to move very slightly in the mid-line and the post-nasal space was occluded'.

Case 7. Bilateral External Rectus and Facial and Unilateral Palatal Palsy, Micrognathia, Stridor, Imperfection of Primary Teeth, Klippel-Feil Syndrome

S.W., a girl, was born in 1947. She was the second child of parents who were not related by blood; the father was healthy; the mother was said to have congenital and rheumatic heart disease, and her mother had twin siblings, one of whom died at birth while the other was said to be 'double inside, with a double brain; very clever—an infant prodigy, but it was known that he would die, and when he was 5 he did'.

The mother was not ill during pregnancy, but her small size was a matter of comment and she had a stitch in her left side throughout; these features suggest oligamnios and increased pressure (Browne, 1936). Labour was one month premature but not otherwise abnormal; the baby weighed 4½ lb.

She was brought to hospital at 10 weeks with the complaints that she could not cry aloud, breathing was noisy, and she could not suck from the breast. The chin was very small and the tongue was bunched up to the palate, in the middle of which there was a small white nodule. The cry was hoarse and difficult; there was inspiratory stridor with suprasternal and lower costal recession. The neck was short. The left side of the chest, face and cranium were flattened anteriorly, and there was corresponding flattening on the right posteriorly, but this is so common a minor deformity that it was probably unrelated to the other abnormalities.

The symptoms were ascribed to the micrognathia, in which condition the falling back of the tongue may indeed produce noisy dyspnoea, but the character of the cry suggested that the stridor might be laryngeal, and in fact, it persisted for three years, long after the symptoms of micrognathia with 'tongue-swallowing' had gone. The voice is still hoarse at 4 years. Radiographs showed (at 10 weeks) adequate oral, nasal and pharyngeal airways, but the upper 5 mm. of the lumen of the larynx appeared to be only 1 mm. deep, enlarging in the next 7 mm. to a normal size. The trachea looked normal.

The head appeared to be resting on the shoulders, and the cervical vertebrae were fragmentary. The heart and lungs appeared normal but the cranial bones were very thin.

She grew fairly well and is at 4 years of normal size allowing for the prematurity. She sat, walked, and talked late, and was thought to be mentally defective, but it is not yet certain how much inability to move the eyes, face, or neck adequately has contributed to this impression.

As is usual in cases of congenital paralysis of the external recti, convergent squint developed at the age of 9 months. In infancy the face did not move, but at 4 years the upper eyelids move slightly when she tries to shut her eyes, and there is some lower facial movement especially on the left. The palate moves poorly on the right.

As the milk teeth erupted, it was noticed that each had black marks; the canines were sharply pointed; enamel had worn off the upper teeth when she was 3½ years old, and since then many upper and lower teeth have been extracted because of severe caries.

Case 8. Bilateral Oculomotor and Unilateral Facial and Lingual Nerve Palsy, Micrognathia, Stridor, Imperfect Primary Teeth

B.S., a boy, was born in 1947. He was the first child of healthy parents not related by blood; there was no illness during pregnancy; delivery was normal but three weeks premature; he weighed 6 lb. 9 oz. He had an umbilical infection which was treated in hospital. At 4 weeks he was again in hospital on account of difficulty in feeding, inspiratory stridor, and attacks of cyanosis. There was bilateral epicanthus; the mandible was very small.

At 3 years he was undersized but well. Dr. W. G. Wyllie saw him and noted right facial palsy and divergent squint; to look forward the boy turned his head to the right and used the left eye, in which there was a small subconjunctival cyst on the medial side. There was some hypermetropia.

He walked and talked late but did not appear by his actions to be mentally backward. At 5 years stridor was still quite loud when he had a cold. His face was expressionless, but when asked he would shut his left eye, and the left side of the mouth moved when he showed his teeth. When he cried the right side of the mouth moved, but not the upper facial musculature. There was right ptosis. The mandible was small but not truly micrognathic; its growth had been noted with pleasure and surprise. The tongue was protruded to the right. Gross dental caries developed in his fourth year, and most of the teeth were soon brown stumps.

Case 9. Bilateral External Rectus and Facial and Unilateral Oculomotor and Lingual Palsy, Micrognathia, Anomalies of Right First and Second Ribs

D.B., a boy, was born in 1939. He was the fourth child of healthy parents who were not related by blood; there was no illness during pregnancy; birth was difficult and long, but instruments were not used. Paralysis of the left side of the face was noticed soon after birth, but it lessened rapidly although slightly.

At five months he was seen by Dr. W. G. Wyllie who noted the small, underhung lower jaw, deficiency of facial movement, small size of the left side of the tongue, and weak cry. A convergent squint developed during the first year. It was later determined, by Mr. J. H. Doggart, to be due to paresis of both external recti with some weakness of the right internal rectus, and was treated surgically.

He was followed for years, and did well; at 13 years the face in repose is not unsightly, but the facial, oculomotor and left lingual paresis persist. There is no loss of sensation on the face, or of taste on the anterior two-thirds of the tongue. The mandible does not now appear small.

Clinical Features

The clinical features of facial diplegia have been reviewed in many previous publications, and will not be repeated here, but some points, illustrated by my cases, perhaps deserve more attention than they have received elsewhere. The first should be obvious, but in practice it has not been; it is that the lack of expression may suggest an unfounded diagnosis of mental defect. The infant who does not smile and laugh in response to his mother's endearments is thought to be dull, and if his apparent indifference is reinforced by failure to follow moving objects with his glance, the impression is strengthened. Later on weakness of the palate or tongue as well as the face may delay the acquisition of speech and add further weight. Dribbling is another unattractive feature in patients with oral paralysis. Case 5 (I.Q. 85), Case 6 (I.Q. 104), and perhaps Case 7 suffered in this way; in Case 9 the physician who referred the 5-month-old child from the welfare centre to the hospital noted that 'he follows the finger well and is quite bright, plays with his toys, etc.' but at 15 years he was still suffering at school from the nickname 'Dopey'.

In discussion of these cases doubt has been expressed at the statement that there has been some improvement in the abnormalities, because they are congenital and thus are supposed to be fixed for ever. Yet development of an organ or tissue does not come to a standstill at birth, and there seems to be no reason why an abnormal tissue should not develop somewhat. Just after birth the facial muscles are limited in expression to the grimace associated with crying, and full animation is not achieved for several years, so it is not necessarily surprising that in Cases 2, 5, 7, and 9 some increase in mobility occurred. Eye movements are limited until the baby can "fix" with his eyes, but this is learnt at a comparatively early age and in my cases

no improvement in ocular mobility was noticed; on the contrary squint, absent at first, only became apparent as use of the eyes developed during the first year. Movement of the palate and tongue is imperfect in early life (for example, babies cannot separate them in order to breathe through the mouth for several weeks or months), and improvement in tongue or palate was seen in Cases 3 and 4, and might have been found in others if they had been observed closely when their feeding difficulties were being overcome.

Micrognathia (Cases 4, 6, 7, 8 and 9) is not recognized as a constituent of the facial diplegia syndrome, although it is apparent in some of the pictures of the younger patients (e.g., Spatz and Ullrich, 1931; Danis, 1945). Normally the proportions and shape of the mandible change greatly with age, so it is not surprising that mandibular hypoplasia becomes less obvious (e.g., Cases 8 and 9). A similar change occurs in Pierre Robin's syndrome of micrognathia and cleft palate (Pruzansky and Richmond, 1954; O'Brien, 1954). Stridor also is not commonly recognized as an associated feature and it too decreases with age (Cases 4, 7 and 8). It is difficult in these babies to decide quite certainly whether laryngeal deformity, displacement of the tongue or epiglottis produced by muscular weakness, or even defect of the intrinsic muscles of the larynx produces the stridor.

The Klippel-Feil deformity of the neck appears not to have been described hitherto as an associate of facial paresis.

Association of the Lesions

The bizarre association of the cranial nerve palsies are a challenge to the impulse to conjecture.

> ' Toute science physique résulte essentiellement de deux ordres de faits: les faits particuliers, que révèle l'observation; les faits généraux, que le raisonnement fait découvrir. Embrassés dans de communes études, ils se fécondent, se vivifient mutuellement.' (Saint-Hilaire, 1836.)

If the abnormalities of cranial musculature are produced by nuclear agenesis it is odd that the eleventh cranial nerve, and possibly also the fourth, are spared, as are the sensory nuclei also. The nuclei that are affected have no close embryological connexion for they arise in all three of the motor divisions—somatic, branchial and splanchnic. There may be some unknown metabolic connexion between them, but there is no consistent anatomical linkage, and their nerves also follow different paths. The type of paralysis is surprising; instead of the supranuclear lower facial paralysis, or the nuclear paralysis affecting both the upper and lower face, we find the upper part more affected than the lower. Again, it is an odd third nuclear palsy which consistently leaves the intrinsic muscles of the eye unaffected.

One can but wonder whether the nuclei are in the first place involved at all. The pathological investigation of three cases by Heubner (1900), Rainy and Fowler (1903) and Spatz and Ullrich (1931) showed that nuclei and nerves were hypoplastic or absent, but this need not be a primary abnormality. If muscle does not develop its nerve is atrophic; Dunnebacke (1953) regarded it as 'well established that the quantitative development of the first sensory or motor nerve centres is controlled by their peripheral fields'. She illustrated this by removing the primordium of the superior oblique muscle in chick embryos two and a half days before the trochlear fibres would be expected to grow, a procedure which was followed by gross reduction in the cells in the trochlear nucleus although the full number had already developed. Finally, there is no obvious reason why agenesis of certain cranial nuclei should be so often associated with abnormalities of hands, feet, chest wall (pectoralis major, ribs, breast) or jaw.

It is perhaps worth suggesting that the congenital facial diplegia syndrome is probably not due to nuclear agenesis, but the mere hesitant negative would be a dull conclusion. George Sand wrote that 'classification is Ariadne's clue through the labyrinth of nature' (Maurois, 1953) and we might reclassify Möbius' syndrome simply as a congenital defect of muscles.

The muscles concerned are those moving the eye, jaw, palate, face and tongue. With few exceptions (e.g., the external rectus) we do not know what individual muscles are defective, for we are concerned with clinical states such as almost complete ophthalmoplegia externa, asymmetrical movement of the palate, weakness of bite, lack of facial movement except for a little at the angle of the mouth, or wasting of the tongue with failure to protrude it. For example, our observations do not tell us whether defect of the levator or of the tensor palati is responsible for weakness of the palate on one side, yet the tensor is reported to develop in relation to the first branchial arch, the levator to the third and fourth.

There is no complete agreement about the origin of the cranial muscles (Hamilton, Boyd and Mossman, 1945; Keith, 1948). If we spread them as widely as possible we find eye muscles coming from pre-otic somites (at least in the shark), jaw muscles and tensor palati from the first arch, face muscles from the second, levator palati from the third and fourth, and tongue muscles from the three post-

occipital segments of the head. This leaves an awkward gap with the sternomastoid and trapezius arising from the second and third branchial segments but unaffected in Möbius' syndrome.

The adoption of some of the other theories permits much condensation; all the muscles affected might arise from only two branchial segments. It is accepted that the facial musculature arises in connexion with the second (hyoid) arch, and some assert that the external rectus muscle is derived from the facial, thus linking the two common pareses of Möbius' syndrome. Ignoring the levator palati, the rest can be linked to the muscle plates of the first (mandibular) arch and its premandibular process—the tensor palati and the jaw-closing muscles (the masseter and medial pterygoid; Last, 1954) as well as the oculomotor muscles supplied by the third nerve. This leaves only the lingual muscles which, 'according to most authorities appear in the mesenchyme of the developing tongue' (Hamilton *et al.*, 1945), itself a product mainly of the first arch, with contributions posteriorly from the second, later overlaid by the third.

Thus by selecting opinions to suit the case, one may argue that all the pareses found in the syndrome are due to interference with the development of the muscles of the mandibular and hyoid arches. These muscles are differentiated towards the end of the second month of intra-uterine life, and the sparing of the iridian and ciliary muscles is at once explicable, for they develop from the ectoderm and mesoderm of the optic cup much later, in the fourth month. The levator palpebrae is also a later differentiation, in the third month, but it is delaminated from the superior rectus (Keith, 1948) and it is deficient (or at least inactive) when there is complete opthalmoplegia as in the right eye in Case 8.

The associated abnormalities have still to be considered. Mandibular hypoplasia might be expected to occur with hypoplasia of muscle arising in connexion with the mandibular process; the cause of the stridor is obscure clinically and is perhaps sometimes produced by weakness of the tongue, but in Case 7 the long duration of the stridor and the observation of narrowing of the upper part of the larynx, with a normally active tongue, point to actual laryngeal abnormality which may possibly be due to deficient growth of the hyoid arch. The styloid process, a derivative of this arch, could not be seen radiographically when it was sought in this patient.

Other abnormalities were brachysyndactyly of the hands, deformity of the ribs, talipes equinovarus, epicanthus, and fragmentation of the cervical vertebrae. Talipes occurred in 37% of 62 cases surveyed by Danis (1945), and in 16% the hands were deformed. Defects of the chest wall were also common (18%), especially absence of the sternal head of the pectoralis major. This is the commonest of all congenital deficiencies of muscle (Bing, 1902) and cases of its association with brachysyndactyly have been noted by several writers (e.g., Poland, 1841; Bastian and Horsley, 1880; Schwalbe, 1906; Bing, 1939; Soderberg, 1949). Both are anomalies of development of the upper limb bud, one at its base and the other at its apex. Talipes might be produced by abnormality of growth of the lower limb bud.

To explain the coincidence of hypomandibulism, defective growth of cranial muscles and disturbance in different parts of the limb buds is not easy and will not here be attempted in detail. Some of the possibilities which need consideration are as follows:

Genetic. Genes being chemical units act chemically, so that there may be tissue-specific genes (Grüneberg, 1947) but in this condition muscle alone is not affected; cartilage and bone are also involved. The hereditary aspect has not been much studied but such an influence is not obvious, although Danis (1945) found a familial history in five out of 81 cases. The genetics of this condition might repay study, but even if inheritance were shown to be the governing factor we should still be left with the problem, physiological and anatomical, of how the abnormalities were produced by the genes.

The Time Factor. Stockard (1921) showed that interference with the metabolism of fish eggs produced various abnormalities, depending on the time of the interference; this was elegantly demonstrated by Duraiswami (1950) in his experiments on the injection of insulin into hen's eggs. Interference with growth of the limb buds for a short time at the end of the second month might produce symbrachydactyly, pectoral defect and abnormality of the feet. This is just the time when the muscles of the visceral arches become differentiated, and the mandible begins to ossify. Here indeed is a connexion, but it is hard to see why other things which are then developing rapidly are not also affected. The clavicle starts to ossify at the same time as the mandible but grows normally; the cornea, anterior chamber and pupillary membrane form then but are in these patients normal, and so on. Lack of symmetry of the abnormalities which are found is less objectionable, for the position of the embryo may alter the degree of malnutrition of similar tissues on either side.

Multipotent Tissue. The neural crest (Hörstadius, 1950) contributes to the formation of a remarkable variety of organs, and a case could be made for supposing that interference with the growth of the cranial part (of which the human development was described by Bartelmez and Evans in 1926) would produce defects of the mandible, larynx and cranial muscles, and possibly the vertebral anomalies seen in Case 7. This would, however, leave the limb deformities unexplained, and they are so common that they cannot be ignored. Nevertheless, it is interesting to note the resemblance between examples of slight otocephaly, which alone would be viable, and the micrognathia of the congenital facial diplegia syndrome. In otocephaly (Saint-Hilaire, 1836) which occurs in several species including man, the mandible does not develop so that (broadly speaking) the ears subside to a place under the face instead of behind it; in severe cases there is a cyclops eye or even an absent head with a solitary ear in its place (O brave new world, that had such voters in't). The mildest degree shows only 'more or less reduction of the size of the lower jaw', in others there are abnormalities of the tongue and eye muscles, there is hypoplasia of jaw muscles, and in many strains (of guinea-pigs) club foot is common (Wright and Wagner, 1934). The basic factor may be inhibition of the anterior medullary plate and associated ectodermal placodes, which would interfere with the formation and migration of cells from the neural crest. Nevertheless, Wright and Wagner point out that in otocephaly the primary effect is on cartilage, secondary on muscle, whereas it appears that in the congenital facial diplegia syndrome muscle may be affected without gross change in structures which originate in cartilage.

The Bonnevie-Ullrich Syndrome. Having embarked on the dangerous waters of analogy we must face this concept. The story of its evolution may be compressed. Bagg and Little (1924) found in the offspring of *x*-irradiated mice some which showed abnormalities of paws, eyes, hair and kidneys; Bagg (1929) examined such mice *in utero* and found that the diverse deformities of the paws depended on interference with the blood supply by subcutaneous blebs; Bonnevie (1934) showed that the blebs arose where cerebrospinal fluid first escaped from the fourth ventricle (Weed, 1917) and, presumably because of over-production or under-absorption of fluid, travelled along lines of least subcutaneous resistance to limbs, back, etc. Unhappily Jost (1953) has cast a shadow of doubt over Bonnevie's observations, but has shown that in rats amputation of limbs and micrognathia may follow the development of blebs, into which bleeding occurs, produced by treating the mother with pitressin or adrenalin between the 15th and 18th days of pregnancy. This work opens a new vista.

Ullrich, in 1930, described a child with cranial nerve palsies and other abnormalities; in 1938 he adapted Bonnevie's concept to explain this and similar conditions, including pectoral defect and symbrachydactyly (Ullrich, 1949). Henderson (1939) rejected this explanation of agenesis of cranial nuclei, but if it is the muscles and not the nuclei which are primarily affected, his argument is irrelevant. One must admit that myelencephalic blebs might travel subcutaneously to the branchial arches and the limb buds after the seventh week of intra-uterine life, when the choroid plexuses are formed. It happens in the mouse, it might happen in man.

Summary

Nine cases of the congenital facial diplegia syndrome are described. In addition to facial paresis, they showed weakness of ocular, mandibular, palatal and lingual muscles, as well as micrognathia, stridor, epicanthus and abnormalities of the hands and feet.

Some of the abnormalities may decrease with age.

The particular association of the abnormalities is difficult to explain if the pareses are due to nuclear agenesis; congenital deficiency of muscles developing in connexion with the first two branchial arches is more probable.

All the major defects are of structures which are differentiated at the end of the second month of intra-uterine life. How they become malformed is unknown; Ullrich's suggestion that the migration of myelencephalic blebs (described in mice by Bonnevie) does the damage cannot be directly proved in man but might be true.

Dr. W. G. Wyllie first interested me in this condition. He introduced me to several of the patients, Mr. Denis Browne to another. Professor T. B. Johnston pointed out some mistakes but is not responsible for any that remain; Dr. P. E. Polani's suggestions have been helpful.

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THE EARLY MANIFESTATIONS AND COURSE OF DIPLEGIA IN CHILDHOOD

BY

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During a recent survey of children suffering from cerebral palsy in Edinburgh it was found that diplegia was relatively infrequently diagnosed before the age of 2 years. The average delay between the doctor seeing the child for the first time, on account of manifestations of diplegia, and the diagnosis being reached was over one year. The classical picture of diplegia presented in the textbooks is of a child affected by rigidity, spasticity and contractures of the limbs, and only when these features were present was the diagnosis made in the majority of patients. Yet the symptoms and signs of the earlier stages of diplegia are typical and should enable the diagnosis to be made in most patients long before contractures have occurred. In the present paper the early manifestations and course of diplegia will be discussed.

The terminology and classification used during the survey has been described in an earlier article (Ingram, 1955). The term diplegia is used to describe a condition of more or less symmetrical paresis of cerebral origin, more severe in the lower limbs than in the upper and dating from birth or shortly after. Mental deficiency, epilepsy and strabismus are frequently associated findings. Patients suffering from diplegia associated with cerebellar ataxia are not considered in this article.

The Case Material

The findings described in the present article are those of 79 patients with diplegia who were ascertained during a survey of children suffering from cerebral palsy in Edinburgh during 1953. They varied in age from a few weeks to 15 years and included 49 males and 30 females, figures which give a similar sex distribution to that found by Asher and Schonell (1950). The cases were ascertained from a very large number of sources and the incidence found was 0·75 cases of diplegia per 1,000 of the population under the age of 15 years. This figure is somewhat higher than similar incidence figures obtained by other regional surveys. It seems probable that the patients may be regarded as being representative of children suffering from diplegia in the community.

The diplegia was thought to be of congenital origin in all but one of the 79 patients, and the first manifestations had been noted in 64 by parents or guardians before the children were 18 months old. Fifty-eight of these patients were taken to their doctors before this age, yet the diagnosis was reached in only 18 by the age of 18 months and in 45 by the age of 2 years. In 14 patients the diagnosis was reached only when the child was over 4 years old (Table 1).

TABLE 1

AGES AT TIME OF FIRST SIGN OF ABNORMALITY, THE CORRECT DIAGNOSIS, FIRST VISIT TO DOCTOR AND FIRST CLINIC REFERRAL IN 79 PATIENTS WITH DIPLEGIA

Age	First Abnormality Noted by Parents	First Visit to Doctor	First Clinic Referral	Correct Diagnosis
Under 6 months	31	23	8	3
Over 6 months, under 1 year ..	23	10	12	1
Over 1 year, under 18 months ..	10	25	12	14
Over 18 months, under 2 years	11	12	12	27
Over 2 years, under 4 years	2	7	26	19
Over 4 years ..	0	0	8	14
Unknown ..	2	2	1	1
Totals ..	79	79	79	79

The Stages of Diplegia

The majority of patients with diplegia do not show the classical picture of muscular rigidity or spasticity until some time after birth. In fact, after the immediate effects of marked prematurity or birth trauma have worn off the babies are frequently regarded as being normal, even when carefully followed up by infant clinics. That there should be a delay, sometimes of months, in the appearance of dramatic symptoms and signs has led some authors

to state that diplegia is frequently a condition of post-natal aetiology.

Unfortunately few of the classical authors studied the early stages of diplegia closely, though a few showed some interest in its early manifestations (Little, 1862; Parrot, 1873; Lovett, 1888; Osler, 1889). More recently, however, increasing attention has been focused on the nature and significance of postural reflexes which are transiently present in normal infants but which tend to persist, sometimes for years, in children suffering from diplegia. It has been increasingly realized that the neurological findings, and especially the postural reflexes, change as the patient grows older and as his nervous system matures (Bobath and Bobath, 1950).

The change from the infant of a few weeks old who shows little demonstrable abnormality on neurological examination to the child 2 or 3 years old with flexion contractures of all four limbs is a gradual one. But the sequence of changes that occurs in the neurological findings marking the child's progress to this crippled state is remarkably constant. For the purposes of description three stages may be recognized in the gradual development of this final picture of spasticity with contracture of the limbs: the hypotonic stage, the dystonic stage and a third stage in which rigidity and spasticity are present together in varying degree.

The Hypotonic Stage. In the first few weeks after birth the majority of children with diplegia show little obvious abnormality related to the neurological disorder. From the mothers or guardians of the 79 patients in the present series, however, a history was obtained in 31 which suggested that the infants were hypotonic in the first weeks after delivery. 'His head flopped all over the place.' 'He felt like a half-filled pillow for weeks and weeks', were typical comments. At the same time a high proportion of patients were noted to show a marked poverty of movement. The child would retain any position in which he was laid down for many hours. 'He was so still, you wouldn't think he had breathed all night,' said one mother.

Five diplegic patients have been examined in the stage of hypotonia; one of these is included in the series and four are excluded, because they lived outside Edinburgh or were born after the survey was completed. Poverty of movement was observed, especially in the trunk and proximal parts of the limbs. Apart from small-range, feeble finger movements, the patients were very still. On passive movements of the limbs and when the children were held in the arms generalized muscular hypotonia was evident. In all five children the Moro responses and grasp reflexes were more clearly defined and easily elicited than in normal children. The tonic neck reflexes were not exaggerated, and appeared to be less marked than normal in two of the patients. The duration of the stage of hypotonia is very variable and patients were encountered in this stage whose ages varied from 6 weeks to 15 months. In 28 of the 31 patients in whom a history of a hypotonic stage was elicited it lasted between six weeks and six months.

The Dystonic Stage. At about the time the diplegic child first attempts to hold up the head a change occurs in this picture of little apparent abnormality. The mother finds that when she changes the child's position abruptly, especially when dressing or washing him, he suddenly becomes stiff in her arms. The neck and back are extended. The upper limbs are adducted and internally rotated at the shoulder, extended at the elbows, pronated at the forearms and semiflexed at the wrist and fingers. The lower limbs are extended, adducted and somewhat internally rotated at the hips, extended at the knees, plantar flexed at the ankles and flexed at the toes (Fig. 1). This position, essentially one of opisthotonos, is achieved by a sudden dystonic movement of the trunk and neck associated with extensor movements of the limbs.

FIG. 1.—The position assumed during dystonic attacks by a severely affected diplegic child aged 15 months.

The position is maintained for only a few seconds, during which time the tone of the muscles is very greatly increased and the whole child is rigid. Sometimes there appears to be a slight impairment of consciousness during the attacks but it is never lost. Initially the attacks occur only once or twice a day, but over the course of one or two weeks their frequency increases. They become more easily produced and may occur as often as 20 or 30 times a day, greatly distressing the child. Frequently dystonic attacks are diagnosed as being epileptiform but they respond to none of the commonly used anticonvulsive drugs.

On examination at the height of the dystonic stage, it is usually found that the child is beginning to hold up the head, but is still unable to hold it steadily. He makes little attempt to reach for objects and poverty of voluntary movement is still evident. The tone of the limbs remains hypotonic at rest. The grasp reflexes are brisk. With care not to extend the head suddenly the Moro responses may be demonstrated in most of the patients. When the child is held vertically there is rigid increase of tone in the limbs. This is more marked in the lower than in the upper limbs. The lower limbs show a position of extension at the knees and plantar flexion at the ankles. The hips are adducted, slightly internally rotated and may show a position of full extension or of a few degrees of flexion. The legs may scissor. When the child's head is briskly extended, or he is suddenly rotated into the horizontal position from the vertical, supported by a hand in the small of the back, there is a sudden gross increase of tone in the trunk and limbs, associated with a quick, writhing, dystonic movement of the trunk. The limbs extend and a position of opisthotonos is assumed for a few seconds. This position corresponds exactly with that described by the mothers as resulting from changes in the position of the child when she handles him.

After a variable period the dystonic attacks become less easily produced and less frequent. In the majority of patients the generalized dystonic attacks are present for between two and six months, but in others the period may exceed one year. As the attacks begin to be less frequent the mother notices for the first time that the limbs are constantly rigid. This is first evident in the thigh or calf muscles and she may find that she has to use force to separate the thighs when placing the napkin, or even pass it between them on the end of a pencil. When she washes the lower limbs they feel stiff and unyielding. In the course of a few weeks the rigidity becomes increasingly evident and spreads to involve the upper limbs in triplegic and tetraplegic cases.

On examination during the period when dystonic attacks are waning a constant muscular rigidity is found, which is more severe in the lower limbs than in the upper. In the majority of patients sudden extension of the head still gives rise to a typical dystonic attack. In a few patients, however, it is necessary to extend the head and put pressure on the soles of the feet before dystonia is produced. When the child is made to exert himself, or is distressed, the affected limbs tend to assume extensor positions even if true dystonic movements of the trunk have ceased to occur.

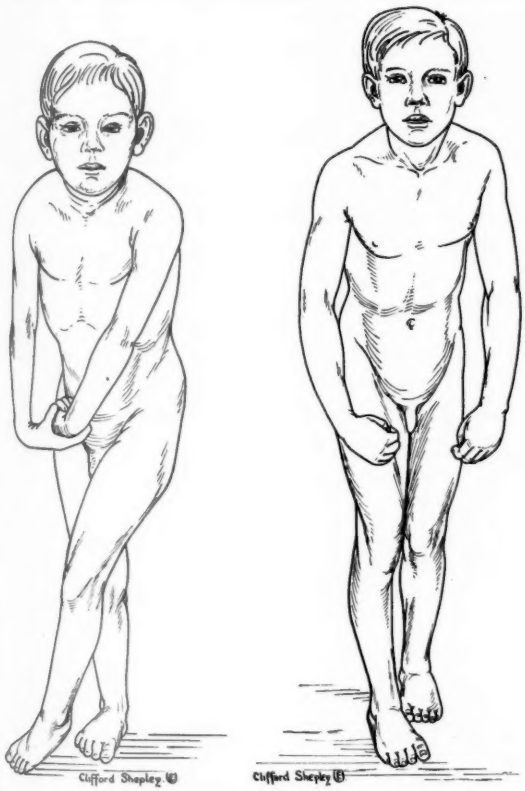
During the survey six patients were classified as being in the dystonic stage of diplegia. Another seven with dystonia have been seen who are not included in the survey. In all, the essentially opisthotonic position described above could be produced by suddenly extending the head and putting pressure on the soles of the feet. Of the 79 children with diplegia in the survey, 39 had evidence of having had dystonic attacks, either in the history or on examination. It was noted that a history of dystonia was found much less frequently in older children than in younger and it is probable that if mothers' memories had been longer a greater number of patients who had had dystonic attacks would have been ascertained.

The Phase of Rigidity. The third stage of diplegia is conveniently divided into two phases for the purposes of description, first the phase of rigidity and secondly the phase of spasticity.

As has been described, the phase of rigidity emerges gradually from the stage of dystonia and for a period, as rigidity increases in extent and severity, dystonic attacks persist. Somewhat arbitrarily the phase of rigidity may be said to begin, for purposes of classification, when generalized dystonic attacks involving the neck, trunk and limbs cease to occur as a result of changes in the child's position. This is usually about the time he attempts to sit with support with the knees flexed and is beginning to use the upper limbs in order to reach for objects. The parents notice that the attempts to grasp are clumsy and that the child appears to hold toys at arm's length with the affected upper limbs extended. In the majority of the patients in the series generalized dystonic attacks ceased between the ages of 5 and 12 months.

On examination children with predominant rigidity show clumsiness of voluntary movements. Manipulations with the hands are immature in type, all the fingers being used together as a unit opposed to the palms. The limbs tend to be held in positions of mild extension at rest, but this tendency is greatly

increased by exertion, the performance of voluntary movements, extension of the head or pressure on the soles of the feet, especially when the child is held erect. When an affected upper limb is moved voluntarily it tends to adduct at the shoulder, extend at the elbow, pronate at the forearm and flex at the wrist and fingers. This is the reason for the impression that the child is holding objects



2a 2b

FIGS. 2a and 2b.—Tetraplegic children, aged 4 and 6 years respectively, showing the extended positions assumed by the limbs in the phase of rigidity.

at arm's length. If the contralateral limb is also involved it too will show a tendency to attain a similar position to the operating limb and the lower limbs also extend. Thus associated movements of extension are present in all the other limbs when one is used and in all the limbs involved when the child exerts himself by straining or attempting to change his position. These associated movements are similar to those observed in the limbs during the earlier dystonic attacks. In the latter, however, the neck and trunk also took part and the involuntary movement was more rapid, more extensive and more powerful. In the stage of rigidity the involuntary postural activity appears to become more inhibited. Nevertheless it is found that the manoeuvres which were most potent in causing dystonic attacks at the earlier stage are also those which produce associated movements of limb extension most readily. When the child is held in the vertical position great rigidity of the lower limbs is evident and they are held scissored and either extended at the hips or in a few degrees of flexion. The knees are extended, the feet plantar flexed. The rigid increase of tone in the upper limbs is less accentuated and their positions may not be markedly constrained. If the feet are placed on the floor, however, or pressure is applied to the soles of the feet, the involved upper limbs immediately assume a position similar to that found during the earlier dystonic attacks.

Involuntarily the child tends to hold the head well forward with the neck flexed. The maintenance of this position minimizes the danger of sudden head extension occurring, with its consequent reflex extension of the limbs and disturbance of posture (Fig. 2). Walking tends to be impossible for a long time, because this involves pressure on the soles of the feet and whenever a step is taken some extension of the neck is almost inevitable. As a result there is involuntary extension of the lower limbs and sometimes the back, which makes the child lose his balance and is the origin of the extensor thrust, noted by physiotherapists, which may last even into the phase of predominant spasticity. The children usually learn to sit without support with the knees flexed, though not with them extended during the phase of rigidity. Any excessive exertion, however, is liable to result in extension of the lower limbs so that if the child is on a chair he is dragged forwards by pressure of the back of the thighs on the chair edge and pulled to the horizontal position.

During the predominantly rigid phase of diplegia the tendon jerks are usually sluggish and difficult to elicit. The Hoffmann responses are not obtained, and the true Babinski response is hardly ever found. The tonic neck reflexes are positive, but extension of the limbs is much more readily produced than flexion. The grasp reflexes are usually present. The Moro response may be sluggishly present in a few patients but it is never brisk and in the majority it disappears completely during the stage of rigidity.

The Spastic Phase. This phase is apparent only after rigidity of the muscles has been present for some weeks or months. In some spasticity appears only after the child has shown predominant rigidity for many years. Its onset is insidious and is usually apparent about the time the child is beginning to

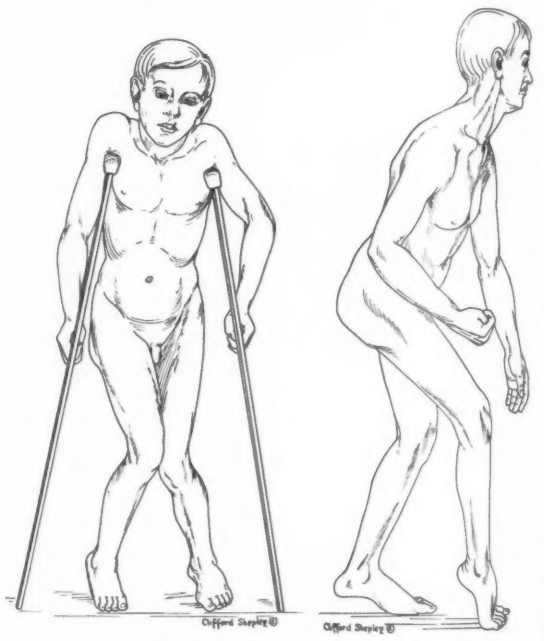
use the thumb and fingers a little and has learnt to sit without support with the knees flexed. Usually attempts to pull himself into the erect position follow shortly after this time.

The first evidence that spasticity has made its appearance is commonly a change in the nature of the associated movements of the limbs which results from voluntary activity or exertion. Over a period of a few weeks the parents notice that instead of being straight the upper limbs tend to be flexed and that all movements are less clumsy and jerky, though they may be slower than before. A grandmother noted, 'His arms used to look as if they'd been put on the wrong way round but then they became all bent up'. The same tendency to flexor positions rather than extensor positions becomes apparent in the lower limbs as in the upper. Unless the child is encouraged in all activities at the stage of early spasticity, especially standing and walking with support, flexion contractures rendering movement impossible can ensue in a few weeks. One nurse in an institution for the mentally defective summarized the position when talking of a bedridden tetraplegic patient, 'First he was too daft to move and now he can't'.

On examination the findings in patients showing spastic increase of tone in the limbs depend very much on the relative severity of rigidity and superimposed spasticity in the individual patient. In patients who remain rigid, associated movements will remain extensor in type, and in patients who show early spasticity flexor associated movements make an early appearance. In the majority of diplegic patients, however, there is a transitional period during which spasticity is increasing in the limbs and the associated movements are neither typically extensor nor typically flexor.

By the time spasticity is well marked in the limbs, not only are the associated movements predominantly flexor but there is also a tendency for the child to hold the limbs in flexed positions at rest. These positions become exaggerated when the child exerts himself. Thus when he walks or attempts to walk there is flexion of the fingers, wrist and elbows, adduction of the thumbs, pronation of the forearms, and adduction and internal rotation of the shoulders in the affected upper limbs. An increase of flexion at the hips and knees, adduction of the thighs and plantar flexion also become evident. The typical walking position of the tetraplegic child results. The legs are scissored, the knees are semiflexed and the heels are not placed to the ground. The child appears to be leaning forwards with the upper limbs flexed across the chest (Fig. 3). When a spastic upper limb is used for grasping athetosis is sometimes evident in the fingers and wrist, though this is not usually marked. Both in the operating and contralateral upper limb the flexor associated movements tend to be most marked at the distal joints in contrast to the extensor associated movements of the rigid phase, which are most marked in the proximal parts of the limbs.

The tonic neck reflex is very marked in the majority of patients in the spastic phase and both flexor and extensor positions of the upper limbs are readily demonstrable in triplegic and tetraplegic cases. The Moro response is absent and the grasp reflex present only occasionally. The tone of the limbs, and especially of the lower limbs, is a mixture of rigidity and spasticity, which gives rise to a very typical feel when they are moved passively. Stretch responses may be demonstrated in the muscles of the affected limbs, first and most easily in the adductors of the thighs and in the calf muscles. The tendon jerks are exaggerated, always to a greater extent in the lower limbs than the upper, and ankle and patellar clonus is frequent. The Hoffmann responses are frequently positive. The plantar responses are extensor bilaterally.



3a 3b

FIGS. 3a and 3b.—Tetraplegic children, aged 10 and 15 years respectively, showing the flexor associated movements and contractures of the limbs in the phase of predominant spasticity.

Once spasticity is evident, contractures in flexion are very liable to occur in the affected limbs (Fig. 3). Contractures give rise to an increase of rigidity

which is accentuated as the limbs are moved passively from the flexed to the extended position, while the earlier rigidity of the limbs tended to be constant throughout the range of passive movement. The contracture is most likely to be severe in the lower limbs in diplegic patients, and it results, when severe, in a great diminution of the stretch reflexes and the tendon jerks. In those all too numerous patients in whom repeated tendon lengthenings, muscle transplants and joint fixations have been performed, the true neurological findings may be further concealed.

The Relationship of the Stages of Diplegia to Each Other

The importance of recognizing that the findings in diplegia change in a regular manner as the condition develops is that this leads not only to earlier diagnosis, but also to better understanding of some of the variations which are encountered in the final clinical picture. The stages of diplegia mark definite milestones in the development of the child's motor control. Thus a child who shows dystonic attacks at the age of 4 years and is, therefore, in the stage of dystonia, must be regarded as showing a very immature motor control. On the other hand, a child in the phase of spasticity has passed through all the stages of diplegia and his neuromuscular mechanisms may be regarded as being more mature, though still disordered. Unless severely affected by contracture, he will be capable of much more in the way of controlled voluntary movement of the limbs than any patient in the stage of dystonia.

The findings in the different limbs of patients with diplegia are not always those of the same stage. Thus it is quite common, even in children aged 10 or 12, to find that one limb is predominantly rigid while the other limbs are predominantly spastic. The child who holds one arm behind his back in the extended position in order to limit the range of its involuntary postural movements while walking and holds the other like a hemiplegic arm across his chest is not uncommon. Almost invariably the spastic limb is the more useful, unless contracture is severe.

It must be stressed that the stages of diplegia are determined by the relative maturity of the child's nervous system much more than by age. Thus one child was seen at the stage of hypotonia at the age of 2 years and one showed spastic diplegia at the age of 10 months. Nevertheless it is of some value to indicate the ages at which the majority of patients show the different stages. Of the 79 children in the present series, a history suggestive of hypotonia was elicited in 31. In 20 of these this stage lasted less than six months, and in 11 less than four months from the time of birth. The dystonic stage was noted in 39 patients. In 29 of these, it was evident before the age of 6 months and in eight between the ages of 6 months and 1 year. Only two patients gave a history which suggested that the dystonia had begun over the age of 1 year. The duration of the dystonic stage was unknown in four patients who were still showing dystonic attacks when the survey closed. In the remaining 35 patients it lasted less than six months in 19 patients and between six months and one year in 11. In five patients the duration of the stage of dystonia was over one year. The age at which rigidity was first evident varied from 10 weeks to three years. In about half of the 72 rigid or spastic patients in the survey, no history of a previous dystonic stage was elicited, though that is not to say that it had not been present.

As has been noted, a few patients showed persistent rigidity throughout their lives without spasticity being superimposed upon this stage. A small number of patients appeared to develop spasticity at a relatively early age without a history of either previous dystonia or rigidity. The majority of patients, however, showed the sequence of stages—hypotonic, dystonic, rigid and spastic—which has been described. It was, therefore, much more usual to encounter cases showing mixed rigid and spastic increase of tone in the limbs than cases showing only rigidity or spasticity.

The age at which spasticity was first evident was even more variable than the age at which dystonia or rigidity first appeared. It was unusual to find spasticity before the age of 8 months, and in the majority of patients it made its first appearance between the ages of 10 and 18 months. On the other hand, the speed with which contracture could cripple the child with spastic diplegia was remarkable. One child was unable to extend either elbow beyond the right angle or pronate either forearm by the age of 18 months, though spasticity had made its appearance only at the age of 11 months so far as could be ascertained from the history.

The Course of Diplegia Related to the Extent and Severity of the Paresis

The severity of diplegia in any case may be assessed roughly by considering the stage of the condition reached at a given age and the extent of the limb involvement. As might be expected, the stages of diplegia are most manifest in patients with severe tetraplegic involvement; they are much less clearly defined in patients in whom the upper limbs

are spared. In particular it is unusual to obtain a history of severe generalized dystonic attacks in paraplegic patients. It seems probable that this is due to the fact that they are much slighter and the duration of the dystonic stage is shorter than in patients with triplegic or tetraplegic involvement. In two paraplegic patients, not included in the survey, dystonic attacks were easily elicited by sudden head extension and pressure on the soles of the feet though in neither was a history obtained which suggested that the children had shown a dystonic stage. In one case dystonia could be produced for only three weeks and in the other for only five. Clearly with slight attacks occurring for such a short period retrospective history taking must frequently fail.

In the present series of 79 patients with diplegia, there was evidence of a dystonic stage either in the history or on physical examination in 19 of the 27 patients with tetraplegia, in 15 of the 23 patients with triplegia and of the 29 patients with paraplegia. At the time of the survey one patient was in the stage of hypotonia, six in the stage of dystonia and 72 were in the stage of rigidity or spasticity. Since the majority of the patients were seen on a number of occasions it was possible to observe the progression of some from stage to stage.

The Early Manifestations of Diplegia

In Table 2 are indicated the commonest initial manifestations of diplegia noted by the parents in 79 patients in the present series. It is apparent that in most cases these should have resulted in a full neurological examination of the patient. If the patient had been fully examined neurologically and the effects of sudden extension of the head been investigated with the child in the erect and supine positions, the diagnosis of diplegia would have been made more frequently at an early age. If diplegia could be diagnosed earlier, before the stage of rigidity or spasticity, the danger of permanent disablement being caused by contractures would be lessened.

TABLE 2
NATURE OF FIRST NEUROLOGICAL MANIFESTATIONS RESULTING IN MEDICAL HELP IN 79 CHILDREN WITH DIPLEGIA

Nature of the Manifestation	No. of Patients
Late milestones or suspected mental defect	20
Poverty of movement or suspected paralysis	9
Dystonic attacks or intermittent rigidity of the limbs	10
Persistent rigidity of the limbs	14
Epilepsy	14
Suspected blindness	5
Behaviour abnormality	2
Other abnormalities	3
Unknown	2
Total	79

Summary

During a recent survey of children suffering from cerebral palsy it was found that the average delay in a diagnosis of diplegia being made following the first visit to a doctor was over one year. This delay appeared to be due to ignorance of the early manifestations to be expected in diplegia before the late stage of rigidity or spasticity with contractures.

The early manifestations of diplegia are described as they were encountered during the survey. It is suggested that the majority of patients pass through a stage during which they show hypotonia and a stage during which they show sudden generalized dystonic attacks on changes of position before rigidity or spasticity is evident. The stage of dystonia seems to be of shorter duration and the dystonic attacks less marked in patients with paraplegic involvement than in those with triplegia or tetraplegia. It is suggested that the diagnosis would be reached earlier in patients with diplegia if a neurological examination, including attempts to produce dystonia, was made in every suspected case.

I am grateful to the many physicians and surgeons in Edinburgh who allowed me ready access to their patients and case notes. I must thank the staff of the Scottish Council for the Welfare of Spastics for their interest and encouragement, especially Dr. Charles Balf, Dr. James Naughton and Miss E. I. Thompson. I am indebted to Mr. Clifford Shepley, artist to the University of Edinburgh, for his most artistic illustrations drawn from many photographs. Miss E. Cruickshank gave much secretarial assistance.

The survey would never have been made without the stimulation and guidance of Professor R. W. B. Ellis. I am most grateful to him, also, for his help in the preparation of this paper.

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A CONTROLLED INVESTIGATION OF ARTANE IN CEREBRAL PALSY

BY

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Drugs have played little part in the treatment of cerebral palsy and none so far have been proved to be of much value. Recently, a group of drugs, trihexyphenidyl and its near analogues, e.g. 'parpanit' and 'artane', have been shown to be useful in Parkinsonism and allied conditions affecting the extrapyramidal motor system. It was considered that these drugs might be of some value in the treatment of infantile cerebral palsy, especially in children with athetosis. It was hoped, however, that some children with the spastic form of cerebral palsy might also benefit, because the lesion is rarely confined to the pyramidal system. When this investigation was planned, no reference had been found to the use of these drugs in cerebral palsy. Corner (1952) demonstrated their favourable effect on two cases of torsion spasm. A little later Melin and Herrlin (1952) reported that they used 'parpanit' in nine cases of cerebral palsy without effect, but 'artane' was successful in relieving increased muscle tone in five cases and was beneficial in one case of pronounced athetosis. Side-effects were minimal. The dose employed was 0·5 mg. gradually increasing to 4 mg. daily.

Present Investigation

In this investigation trihexyphenidyl ('artane') was used. It seemed evident that considerable difficulties would be encountered in the assessment of its effects in cerebral palsy unless precautions were taken to eliminate subjective bias. The plan of the investigation was as follows.

Material and Treatment. Patients suffering from severe congenital cerebral palsy were selected for the investigation and were divided into two groups. One group of 17 patients consisted of 'spastics', with paraplegia, hemiplegia or quadriplegia. The second group consisted of 11 patients with athetosis (including seven cases of kernikterus). Most of these patients had been attending our out-patient clinic and physiotherapy department and the extent of their disability and their rate of progress without treatment with drugs was known. New patients were not included in the investigation until they had received at least two months of intensive physiotherapy.

To ensure an adequate method of control, we requested the makers of 'artane' to supply us with two sets of identical-looking tablets labelled A and B, one being 'artane', and the other an inert substance. Neither the investigator nor the hospital pharmacist knew which were the real 'artane' tablets. The pharmacist was given two sets of envelopes, one for 'spastics' and another for 'athetoids'. Both batches of envelopes contained chits labelled A or B. When a patient was accepted for the investigation 'artane' was prescribed, and the prescription was marked 'spastic' or 'athetoid'. The pharmacist then drew an envelope, and, in accordance with the direction which it contained, she dispensed tablets A or B, keeping the appropriate records in a book. This book was not seen by me until after the analysis was completed.

The dose was gradually increased during the three months from 1 mg. to a maximum of 10 mg. daily, according to tolerance. At the end of three months the child's condition was reassessed and 'reverse artane' was prescribed for the next three months, a child who had had A tablets receiving B tablets and vice versa. The children were then observed for another three months without any drugs* at all.

The parents were told that the children were to receive a new drug which might or might not be of benefit and they were asked to take particular note of the children's general condition, behaviour, and physical and mental progress during treatment. They were also asked to note untoward symptoms. They were not aware that two sorts of tablets were to be used or that at the end of three months the drugs would be different.

Physiotherapy was continued during the investigation, but no other drug was given.*

* Except for anticonvulsants in those subject to fits.

The children were examined by the physiotherapist and by me at the beginning of the investigation and at intervals during and after it, so that their disability could be assessed. When the analysis of the findings was complete, the identity of tablets A and B was determined from the makers.

Results

Spastics. No objective difference in the physical signs could be detected during or after treatment in any patient.

Of eight mothers whose children received 'artane' first, two reported that there was no change, two that there had been slight improvement, three that improvement had been appreciable and one that improvement was marked. Of the nine who received the control tablets first, one did not improve, six improved slightly, and two improved greatly. The improvement lay in an increased alertness and activity and a loosening up of the muscles. None of the children who improved on 'artane' relapsed while receiving the control tablets or during subsequent observation, and none of the children who improved on the control tablets improved more while receiving 'artane' later. One child who improved on the control tablets 'relapsed' while receiving 'artane'. One child on the control tablets and another on 'artane' complained of repeated vomiting.

It was clear that there was no evidence that 'artane', as used in this trial, was of value in these cases.

Athetoids. Many athetoids responded to the treatment much more dramatically than the spastics.

The condition of three children was thought by their parents to be unchanged throughout the trial. Two children were thought to have improved slightly while receiving the control tablets and also while receiving the 'artane'. The improvement continued after the treatment had been discontinued. None of these children showed objective improvement and none had toxic symptoms.

Of the remaining six patients, five had control tablets first. A boy of 13 was said by his mother to have improved miraculously, becoming much livelier and attempting with success tasks, such as dressing, playing or feeding himself, which he had never undertaken before. He showed no objective improvement or lessening of the athetosis. After the end of three months he had no drugs for a few days and he returned to his previous inactive state. He was then given 'artane' and he immediately 'went to pieces'. He became extremely unsteady, was constantly falling and could do much less than before. After two weeks his treatment had to be discontinued and he returned to the condition he was in before the trial started.

Another child, a boy aged 5, was said to have improved in many respects while on the control tablets. He was livelier, but fell more often. There was a dramatic deterioration in his condition when changed to 'artane'. He lost his balance completely and could no longer walk. Treatment had to be interrupted. He then rapidly regained his previous state and has remained much the same since.

The third of these children, a boy of 7, was described as 'grand' while receiving the control tablets and was much steadier. Owing to intercurrent illnesses the experiment could not be concluded.

The fourth, a girl of 3 years, showed slow steady improvement while on the control tablets, but immediately after she started taking 'artane' she became limp, was unable to stand, was very ataxic and the athetosis became more severe. The mother persisted with the tablets in spite of these toxic symptoms for two weeks, but then treatment was stopped and the child made an immediate recovery.

The fifth child, a boy of 12, did not exhibit any change in his condition while on the control tablets, but soon after he started taking 'artane' he also became grossly ataxic, could no longer stand and had severe loss of tone. In addition he had several fits, although he had not been subject to them before. Treatment was stopped and he immediately recovered.

Finally, a girl of 8 with kernikterus started with 'artane' tablets. She exhibited the same toxic symptoms as the preceding cases. The athetosis became much worse and she became grossly ataxic. She had previously been subject to fits, but her fits increased in number and changed their character. She now had severe myoclonic attacks without loss of consciousness. Treatment was stopped and she quickly regained her previous condition.

It should be emphasized that these severe and uniform toxic symptoms in five children all occurred at the beginning of 'artane' treatment when the dose was small, 1-2 mg. daily.

Summary and Conclusions

'Artane' was used in a controlled therapeutic trial in congenital cerebral palsy. Most of the 17 'spastic' children improved while on treatment, irrespective of whether they received 'artane' or control tablets. They all maintained the improvement after the conclusion of treatment.

Five of 11 athetoids exhibited no significant change in their condition whether on 'artane' or on the

control tablets. Two of the remaining six were greatly improved while on the control tablets, two were moderately improved and one remained the same. The sixth did not receive the control tablets. Five of these six patients exhibited dramatic toxic effects while on small doses of 'artane', consisting of loss of balance, hypotonia, increased athetosis and two developed fits. Treatment with 'artane' had to be discontinued in these five. None derived benefit from 'artane' in the dosage employed.

It is a pleasure to acknowledge the cooperation of Dr. A. T. Mennie, Medical Director of Lederle Laboratories, who kindly provided 'artane' and the control tablets for this investigation.

I wish to thank Professor R. S. Illingworth for his criticism, Professor E. J. Wayne, Dr. T. Colver and Dr. R. R. Gordon for access to their cases; Miss L. M. Green, Senior Physiotherapist, and Miss C. I. Crawford, Chief Pharmacist, for their cooperation in this trial.

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EARLY DIAGNOSIS AND EARLY THERAPY IN CONGENITAL CRETINISM

BY

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How soon can the diagnosis of congenital cretinism be made? Isolated cases have been diagnosed at birth (Abels, 1911). There is a photograph in Potter's (1952) monograph showing an infant at the age of 1 month with the typical facies; the case had been diagnosed and, judging by a later view, successfully treated by McIntosh (1952). Wieland (1940), who has great experience, claims that he observed some six or eight cases aged between 3 and 5 months, where the diagnosis was obvious at first sight. All these patients had previously been under the observation of other physicians for symptoms which definitely or very probably were connected with congenital cretinism. Wieland's most successful case, from the therapeutic point of view, was diagnosed and treated from the age of 5 months.

According to Higgins and Ingalls (1948) 'the first signs of cretinism will appear at the age of about 2 months, although the condition is seldom diagnosed before the child is 5 months old'. Many larger series, especially of an early date, contain only few with an early diagnosis and therapy, e.g. Marvel's (1939) from Oslo. A fairly large series from Sweden (d'Avignon and Melin, 1949) with 22 cases includes 10 with a diagnosis made before the age of 5 months.

Why is the diagnosis so often made so late? Frequently the parents do not consult the physician early enough. Another and usual reason is that the physician does not recognize the picture of the disease at its early stage of development. This certainly also applies to paediatricians with great experience. Cases of congenital cretinism are so rare that only one or two per annum are diagnosed at the larger children's hospitals in Scandinavia. Finally, there are cases of mild congenital cretinism where the typical symptoms do not develop until later on, at the end of the first year of life or later.

In a previous paper (Åkerrén, 1954) I have been able to point out the frequent coincidence between congenital cretinism and icterus neonatorum prolongatus with a remarkable duration. In this investigation I combined 10 cases of congenital cretinism which also had shown signs of icterus with a duration of at least six weeks, but otherwise, as far as could be judged, of a physiological type. At an investigation carried out at the Children's Hospital of Gothenburg, including 946 newborn infants who were closely studied for the occurrence and duration of physiological icterus, Beskow, among others, found that the mean duration of icterus which lasted at least 48 hours was $11 \cdot 37 \pm 6 \cdot 20$. A duration of physiological icterus exceeding about 30 days must thus be very rare.

As shown in Table 1, early diagnosed cases of congenital cretinism are unusual. In the table all the cases are given which were admitted to the Children's Hospital of Gothenburg before the age of 1 year, from 1922 up to and inclusive of the spring of 1954. They are in all 18. Of the nine babies admitted before they had reached the age of 3 months, no fewer than six had shown icterus with a duration of at least six weeks. Of the five babies

TABLE 1

CASES WITH CONGENITAL MYXOEDEMA ADMITTED TO THE CHILDREN'S HOSPITAL, GOTHENBURG, BEFORE THE AGE OF 1 YEAR DURING 1922-54

	Cases Admitted		
	Group 1 3 Months Old	Group 2 Between 3 and 6 Months Old	Group 3 Between 6 and 12 Months Old
Cases with prolonged icterus ..	6	1*	–
Cases without any statement of icterus	3	4	4
Total ..	9	5	4

* Had icterus to the age of 2½ months.

admitted between the ages of 3 and 5 months, one had suffered from icterus up to the age of 2½ months.

The coincidence of comparatively unusual conditions, such as early diagnosed congenital cretinism and icterus of a remarkably long duration is not likely to be due to chance.

This coincidence has been mentioned in a few case reports but otherwise not observed or commented upon. The reason seems to be that even experienced paediatricians only rarely get an opportunity of seeing and diagnosing early cases of congenital cretinism. An infant who during the first months of life shows icterus neonatorum of remarkable duration should thus be carefully observed and examined until the diagnosis can be made or excluded with certainty.

Practically all textbooks and handbooks of paediatrics unanimously point out that an early diagnosis and adequate treatment are of greatest importance in the prognosis of mental development in congenital cretinism. The prognosis for the somatic symptoms is, generally, favourable even if the diagnosis is made comparatively late and the institution of treatment is delayed.

When studying publications which give a detailed report of the mental results of the treatment, with consideration to the time of its onset, the picture proves to be less clear and unquestionable. The last series of investigations on prognosis which I have been able to find was published by Topper (1951). The time for the onset of the treatment has there been combined with the I.Q., which was ascertained during a follow-up study. Regarding the mental development, Topper concludes that 'there is considerable evidence to show a lack of correlation between results obtained in the child with congenital hypothyroidism and adequacy of therapy; 7, or 39%, of the adequately treated patients have remained feebleminded in spite of this. These results are not correlated to the onset of therapy'.

d'Avignon and Melin (1949), from a series of 22 cases, come to almost the same conclusion as Topper, viz., that the time for the onset of the treatment is of no greater importance to the prognosis for the psychical development. 'Even when therapy was begun very early, the results were sometimes bad. Correspondingly, there were several cases of classic congenital hypothyrosis in which treatment was begun relatively late and yet the final results were good.'

Radwin, Michelson, Berman and Kramer (1949) found, in spite of considerable difference of the age at which thyroid was first started, that seven patients out of 10 display normal intelligence levels. In some of them therapy had been started as early as 4 weeks, in others as late as 3 years.

The series by Topper, d'Avignon and Melin, and Radwin *et al.* are singly not large enough to be statistically studied. Neither have the authors expressed more exactly what they meant by early therapy. In Table 2 I have combined these three series. I have then excluded the cases where the treatment has been indicated as inadequate, or where the treatment was started later than at the newly reached age of 3 years. One case has been excluded from Topper's series, where the final results regarding the mental development was 'defective', there being a psychosis present, but where the I.Q. was high.

TABLE 2

RELATION BETWEEN THE TIME OF STARTING TREATMENT WITH THYROID AND MENTAL DEVELOPMENT

No. of Cases with I.Q.	Treatment Begun		
	Group 1: Before Age of 5 Months	Group 2: From 5 Months but before 12 Months	Group 3: From 1 Year up to and Including 3 Years
Below 70	2	6	4
70–79	–	2	1
80–89	5	1	2
90–110	8	4	11
110		1	2
Total with I.Q. below 80	15 2 (13·3%)	14 8 (57·1%)	20 5 (25·0%)

The differences between the frequency of an I.Q. of less than 80 in the various groups has been statistically analysed by means of the χ^2 method. Between groups 1 and 2 there is a difference significant at the 5% level. Between groups 1 and 3 and 2 and 3 there is no statistically significant difference.

Judging by the statistical study of the series combined here, it seems justifiable to conclude that treatment started before the age of 5 months gives more hope of a favourable result than treatment begun later on. It may seem remarkable that such a comparatively large number of the results obtained in group 3 are favourable, although these results do not differ in a statistically significant way from those obtained in group 2. This is probably due to the fact that this group is likely to be less homogeneous than the other two. Thus it includes some severe cases where the therapy was begun late with a bad result as a sequel, but it probably also includes some slight cases in which it was impossible to make the diagnosis earlier. In these cases the insufficiency of thyroid has not been severe. The central nervous system and especially the brain have not been

subjected to such early damage from or early after birth as when there is an already severely deficient thyroid function. The results have, therefore, to rather a large extent been successful.

Table 3 illustrates, although it is not sufficiently

TABLE 3
DISTRIBUTION OF CASES WITH I.Q. BELOW 70 TO ONSET OF TREATMENT

	No. of Cases		
	Group 1	Group 2	Group 3
I.Q. less than 30 ..	–	3	–
30–50		1	1
51–69	2	2	3
Total	2	6	4

extensive for statistical studies, the differences in results between the three groups. The table shows that the most severe disturbances with I.Q. below 30 only occur in group 2 and that in no case where the treatment was begun before the age of 5 months was an I.Q. below 51 found.

Summary

There is an obvious coincidence between congenital cretinism and icterus neonatorum of excessive duration. In babies with congenital cretinism who come under observation before the age of 3 months, icterus seems to be very frequent.

The knowledge of this syndrome must be assumed to be of practical importance for the early diagnosis of congenital cretinism. In cases of icterus neonatorum of excessive duration careful observation and examination must be performed until the diagnosis can either be made or excluded.

In cases of severe congenital cretinism early treatment, i.e., beginning before the approximate age of 5 months, gives a much greater chance of obtaining a favourable mental prognosis than if the treatment is started later.

As an early diagnosis of congenital cretinism is a reason for early adequate therapy, the knowledge of the congenital cretinism-icterus neonatorum syndrome is of value from the therapeutic and prognostic points of view.

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PRE-NATAL GROWTH OF MONGOLOID DEFECTIVES

BY

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The literature contains several references to the maturity of mongols at birth. Southwick (1939) noted that the mean birth weight (7·08 lb.) of 108 mongols was only slightly below normal, but in most reports it is stated that affected children are frequently 'premature', although criteria of maturity are not always specified. Nevertheless, there is evidence that the birth weight of mongols is low (Schröder, 1938; Benda, 1939; Øster, 1953), and that the period of their gestation is shorter than normal (Beidleman, 1945; Øster, 1953). The reported data do not, however, permit one to decide whether the low weight at birth is due wholly to the short duration of gestation, or is attributable in part to a reduced rate of pre-natal growth.

To come to a decision on this matter we require to know the mean birth weight according to duration of gestation, both for a group of mongols and for a population of normal births. Information of this kind was obtained in an enquiry in which an attempt was made to trace all mongols born in Birmingham during the 11 years 1942-52. (A fuller description of this material is provided by Record and Smith, 1955.) Two hundred and fifty-two mongols were identified, of whom 120 were born in hospitals. For 103 of the hospital cases data in hospital notes included birth weight and duration of gestation (from the first day of the last menstrual period preceding pregnancy to birth). For 66 of the 103 individuals the weight of the placenta was also recorded.

Although the same observations were not available in respect of the total population of hospital births in the period 1942-52, they were obtained in an earlier enquiry (McKeown and Record, 1953) for 4,931 of the 7,341 single live births delivered in the Birmingham Maternity Hospital during the four years 1946 and 1948 to 1950.

Table 1 compares the weight distribution of the 103 mongols with that of the 4,931 controls; mean weights are 6·38 and 7·10 lb. respectively. For all births (9,699) delivered in Birmingham hospitals during 1947, the mean weight was 7·15 lb. (McKeown and Gibson, 1951), so that although the 4,931 controls are selected from births in one hospital during four years, it seems probable that in respect of weight distribution they are reasonably representative of all hospital births in the city during the 11-year period from which the mongols were drawn. The evidence in Table 1 is consistent with

TABLE 1

COMPARISON OF WEIGHT DISTRIBUTION OF MONGOLS AND CONTROLS

Weight (lb.)	Mongols		4,931 Hospital Single Births (%)
	No.	%	
Under 4 ..	—	—	2·6
4–	3	2·9	1·3
4½–	8	7·8	2·5
5–	8	7·8	4·1
5½–	20	19·4	6·3
6–	15	14·6	11·3
6½–	16	15·5	14·0
7–	16	15·5	17·3
7½–	7	6·8	15·1
8–	7	6·8	11·3
8½–	3	2·9	7·4
9 and over ..			6·8
Total ..	103	100·0	100·0

TABLE 2

DISTRIBUTION OF MONGOLS AND CONTROLS ACCORDING TO LENGTH OF GESTATION

Gestation (weeks)	Mongols		4,931 Hospital Single Births (%)
	No.	%	
Under 31 ..	—	—	0·5
31–	1	1·0	0·5
32–	3	2·9	0·7
33–	4	3·9	0·7
34–	—	—	1·1
35–	5	4·9	2·2
36–	10	9·7	4·4
37–	15	14·5	7·5
38–	21	20·4	12·8
39–	20	19·4	17·9
40–	11	10·7	22·1
41–	8	7·8	17·0
42–	2	1·9	8·1
43–	2	1·9	3·0
44–	1	1·0	1·0
45 and over ..	—	—	0·6
Total ..	103	100	100

other reports that the birth weight of mongols is low.

The low weight is accounted for to some extent by early onset of labour. Table 2 gives the distribution of mongols and controls according to duration of gestation; the means are 268·9 and 278·4 days respectively (279·7 for 8,292 births in all Birmingham hospitals during 1947).

Their short period of gestation does not, however, entirely explain the low birth weight of mongols, which must be attributed in part to a reduced rate of pre-natal growth. In Table 3 mean foetal weight

TABLE 3
MEAN FOETAL AND PLACENTAL WEIGHT ACCORDING TO DURATION OF GESTATION

		Duration of Gestation (weeks)				
		30–	36–	38–	40–45	Total
Foetal weight (lb.)	Mongols	5·52 (13)	6·25 (25)	6·46 (41)	6·84 (24)	6·38 (103)
	Controls	4·67 (266)	6·20 (585)	7·06 (1,513)	7·60 (2,547)	7·11 (4,911)
Placental weight (lb.)	Mongols	1·07 (7)	1·30 (14)	1·36 (28)	1·37 (17)	1·32 (66)
	Controls	1·11 (266)	1·31 (585)	1·38 (1,513)	1·46 (2,547)	1·40 (4.911)

according to gestation is given for 103 mongols, and for 4,911 of the 4,931 controls (20 control births whose duration of gestation was less than 30 weeks or more than 45 weeks are excluded). The numbers of mongols are of course very small for this purpose, but the results appear to justify the conclusion that at least from about the thirty-eighth week of gestation mongols are lighter in weight than unaffected births delivered at corresponding stages of gestation.

Table 3 also gives mean placental weight according to duration of gestation for 66 cases for which the information was available and for controls. The

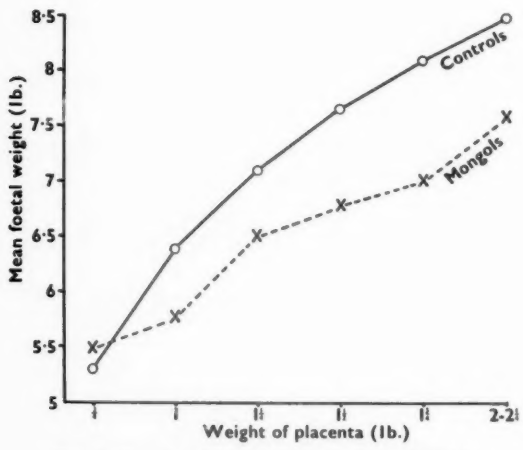

FIG. 1—Foetal weight according to placental weight.

slight differences exhibited in Table 3 do not suggest that the placentae of mongols are lighter in weight than those of normal births. There is, however, a fairly sharp difference between foetal weights at

TABLE 4
MEAN FOETAL WEIGHT ACCORDING TO PLACENTAL WEIGHT

Weight of placenta (lb.)	¾–	1–	1¼–	1½—	1¾–	2-2¼
Mongols . .	5·49 (5)	5·77 (20)	6·50 (22)	6·77 (12)	7·00 (3)	7·58 (3)
Controls . .	5·29 (231)	6·38 (858)	7·09 (1,476)	7·65 (954)	8·08 (447)	8·48 (120)

corresponding placental weights (Table 4 and Fig. 1). At all placental weights greater than ¾ lb. the weight of mongols is substantially lower than that of controls.

These results are consistent with other reports that the birth weight of mongols is low, and that the period of their gestation is shorter than normal. The low weight is not, however, entirely due to the early onset of labour, and, as in multiple pregnancy, must be attributed in part to a low rate of pre-natal growth. But in multiple pregnancy retardation of pre-natal growth is associated with a low placental weight (McKeown and Record, 1953), whereas the placentae of mongols appear to be of approximately normal weight (Table 3). This is not, of course, to say that the placentae are normal in all respects; but in view of the possible significance of the uterine environment in the aetiology of mongolism, it is of interest that the uterus appears to be capable of supporting a placenta of normal weight. The retardation of pre-natal growth of mongols may be due to a lowered growth capacity of the foetus, rather than to the inability of the uterine environment to support its growth. The marked inhibition of post-natal growth (Benda, 1939; Øster, 1953) is consistent with this view.

Summary

Data are recorded on 103 mongols delivered in Birmingham hospitals during the 11 years 1942-52, and on 4,931 single live births delivered in the Birmingham Maternity Hospital during the four years 1946 and 1948-50. In the two groups respectively mean birth weights were 6·38 and 7·10 lb., and mean durations of gestation 268·9 and 278·4 days. The low birth weight of mongols is not entirely explained by the early onset of labour, but must be attributed in part to a low rate of pre-natal growth. The retardation of growth is not, however,

associated with a low placental weight and may be due to a lowered growth capacity of the foetus, rather than to the inability of the pre-natal environment to support its growth.

For permission to examine records we are indebted to the staffs of Birmingham hospitals.

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TUBERCULOUS MENINGITIS IN TWO BROTHERS VACCINATED WITH B.C.G.*

BY

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Bacille-Calmette-Guérin (B.C.G.) vaccination on a large scale was started in a number of European countries in 1947 by the Danish Red Cross, and in the following year this campaign was enlarged under the United Nations International Children's Emergency Fund (Unicef) and became known as the 'Joint Enterprise'. As a result of this scheme, some 8 million children and young adults have been vaccinated with B.C.G. Bearing in mind the Lübeck disaster of 1930 when 73 vaccinated children died from tuberculosis, it is especially important when any large-scale vaccination project is undertaken to be satisfied that the technical arrangements are such that severe complications are unlikely to develop. If complications are encountered the circumstances should be fully investigated because complications might have serious repercussions on future B.C.G. vaccination campaigns, and also on other forms of prophylaxis, such as diphtheria immunization, which have been successful in reducing mortality and morbidity. Up to the present time few serious complications have been reported in children following B.C.G. vaccination, but it is the purpose of this communication to record the development of tuberculous meningitis in two brothers vaccinated with B.C.G., to review the relevant literature, and to discuss the implications.

Case Reports

Case 1. G.W., born on October 31, 1950, was vaccinated with B.C.G. (0·1 ml. of batch 1006) when he was 21 months old. A Mantoux test had been performed 23 days before vaccination and the reaction was negative. His father was suffering from open pulmonary tuberculosis and had been removed to a sanatorium two months previously. Thirty-one days after vaccination the child wanted to be nursed continuously, was generally off colour and developed a cough. One week later he became anorexic and began to lose weight; after a further week he began to vomit, was constipated, developed grunting respirations and had a temperature of 103° F. He was given sulphonamides for four days but no improvement in his condition was apparent. On admission to hospital (52 days after B.C.G. vaccination) he had a temperature of 101° F., pulse rate of 140 and respiration rate of 30 per minute. No definite abnormal signs were present in the lungs or elsewhere. A blood count showed Hb 90%, white cell count 15,000 per c.mm. (80% polymorphs) and the sedimentation rate was 12 mm. in one hour. Lumbar puncture was performed and a clear, colourless cerebrospinal fluid, which developed a spider-web clot on standing, was obtained. The fluid contained 100 mg. % protein, 32 mg. % sugar, 180 cells per c.mm. (90% mononuclears) but acid-fast bacilli were not seen on direct examination. Treatment with intramuscular and intrathecal streptomycin and oral I.N.H. was started and he was transferred to Alder Hey Children's Hospital.

On examination he was a pale, wasted, semicomatose child with marked neck stiffness and a positive Kernig's sign. He had a left facial palsy and spasticity of the right arm and right leg. A small scar was present over the left deltoid at the site of B.C.G. vaccination. The margins of the optic discs were blurred but no choroidal tubercles were seen. The Mantoux reaction was negative at 1 in 10,000 dilution but positive at 1 in 1,000 and a radiograph of the chest showed a primary complex at the right lung base. Lumbar puncture was performed and tubercle bacilli were grown from the cerebrospinal fluid; guinea-pigs inoculated with the fluid developed typical tuberculous lesions; the tubercle bacilli were of the human type and were sensitive to streptomycin and I.N.H. Treatment with streptomycin and I.N.H., which he was having on admission, was continued but his condition deteriorated, papilloedema and spreading of the skull sutures developed, and burr holes were made through which streptomycin was given into the lateral ventricles. His condition further deteriorated and intrathecal P.P.D. was given daily for eight weeks (Fig. 1). He then made slow but steady progress, and with the help of physiotherapy the right hemiplegia improved. The meningitis is now inactive and has remained so during the past 18 months; his vision is normal but he is deaf.

Case 2. R.W., born on December 21, 1946, was vaccinated with B.C.G. (0·1 ml. of batch 1006) when he

* A paper read at a joint meeting of the Birmingham, Leeds, Liverpool and Sheffield Paediatric Clubs at Sheffield on September 25, 1954.

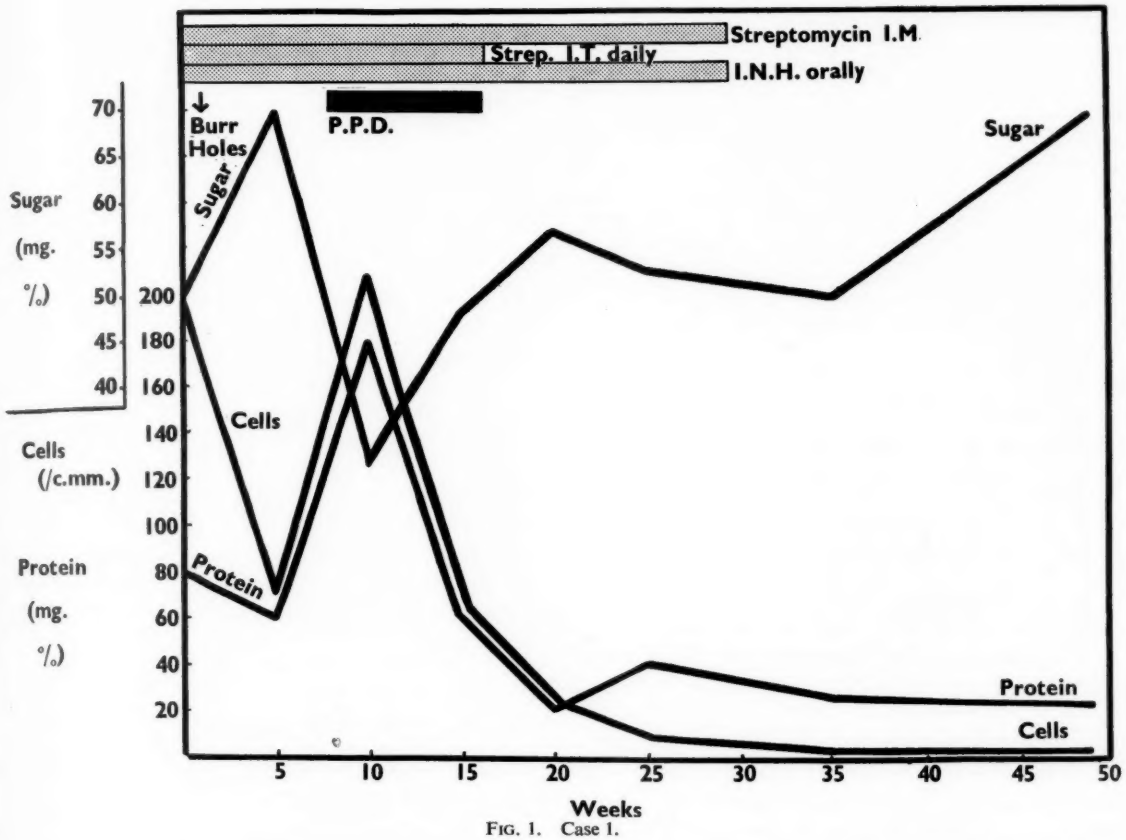

FIG. 1. Case 1.

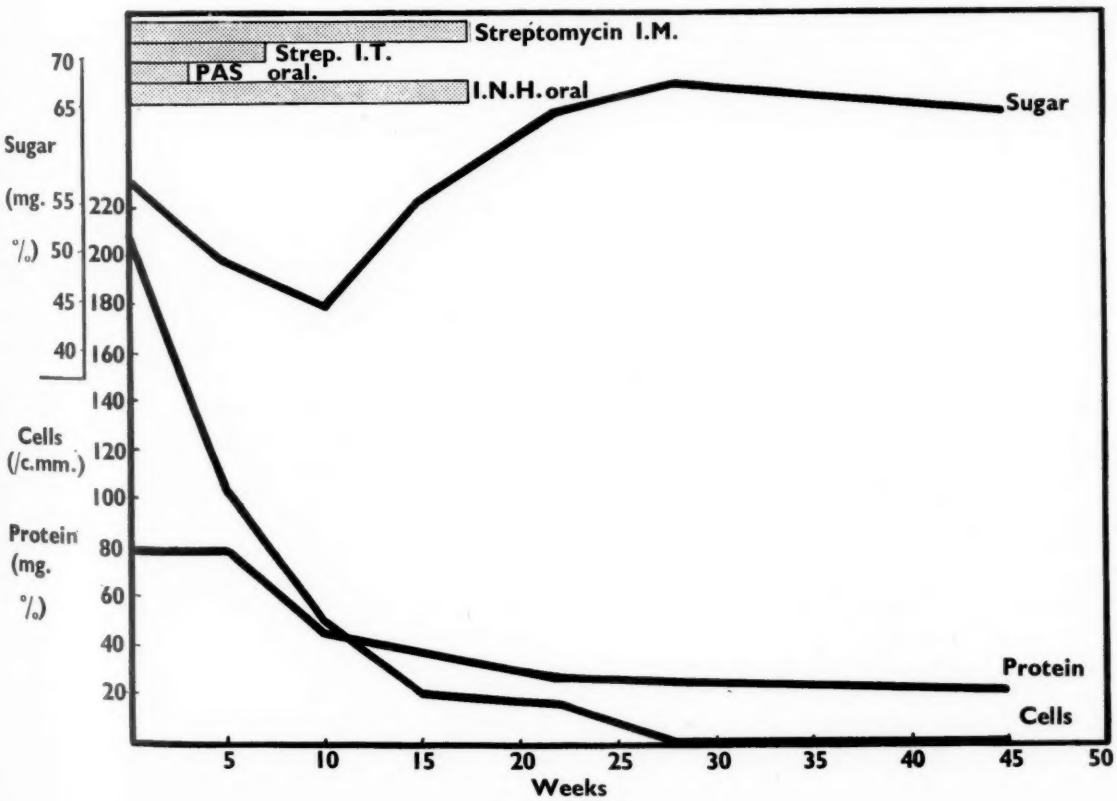

FIG. 2. Case 2.

was 5½ years old, on the same day as his younger brother. A Mantoux reaction 23 days previously was negative, and when seen 54 days after vaccination the Mantoux reaction (1 in 1,000) was positive (erythema 35 mm. in diameter, induration 20 mm. in diameter) and he had a vesicle 6 mm. in diameter at the vaccination site. He had been in good health both before and after vaccination, and he remained well until six months later when, after returning from school, he complained of headache and vomited on one occasion. Two days later he was admitted to hospital with a temperature of 101° F. He was fully conscious, the optic fundi were normal and the only abnormal finding was slight neck stiffness. A chest radiograph showed large glands at the right hilum and shadowing in the right upper lobe. Lumbar puncture revealed a clear, colourless cerebrospinal fluid which developed a spider-web clot on standing. The fluid contained 210 lymphocytes per c.mm., 80 mg. % protein, 58 mg. % sugar, and tubercle bacilli were seen on direct examination. The fluid was cultured but no growth obtained. The fluid was also inoculated into a guinea-pig but the animal died prematurely and showed no evidence of tuberculosis. He was treated with intramuscular streptomycin, intrathecal streptomycin and oral I.N.H. and made an uninterrupted recovery (Fig. 2).

His father, who was in a sanatorium at the time B.C.G. vaccination was performed, had returned home and was sputum-negative following a thoracoplasty, but further investigation of other members of the household previously free from tuberculosis showed that an aunt had radiological evidence of active tuberculosis. It is probable that the boy had been infected recently from this source.

Discussion

The development of tuberculous meningitis in relation to B.C.G. vaccination is a rare occurrence; indeed it is commonly assumed that tuberculous meningitis and miliary tuberculosis do not occur in B.C.G.-vaccinated children. There is indirect evidence that the frequency of these complications is much less in children who have received B.C.G. vaccination when compared with children not vaccinated, but there is no convincing statistical proof. In any large-scale vaccination project isolation of the children to be vaccinated for a preliminary six-week period and for a similar period after vaccination is impracticable. In these circumstances it is inevitable that some of the children will be already infected with tuberculosis at the time of vaccination, although still in the pre-allergic phase in which the Mantoux test is negative. Others may become infected with tuberculosis after vaccination but before this procedure could have any influence upon the development of a tuberculous lesion. The incubation period for tuberculosis is generally regarded as being from 35 to 40 days, but in some recorded instances the lower limit has been 15 days and the upper limit 56 days. If, therefore, a patient presents evidence of tuberculosis within 15 days of vaccination we can conclude that the disease was present before vaccination; if tuberculosis develops more than 56 days after vaccination it is probable that the disease was acquired after vaccination; if evidence of tuberculosis exists 15 to 56 days after vaccination we cannot be sure if it was acquired before or after vaccination. In any event, there is no evidence to suggest that B.C.G. vaccination shortly before or after infection with tuberculosis affects the course of the disease, so that the precise time of development of tuberculosis in relation to B.C.G. vaccination may be purely an academic point and of no practical significance. But the development of a serious form of tuberculosis in close relation to B.C.G. vaccination may influence the public in their acceptance of this form of prophylaxis.

Imerslund (1943) described the subsequent clinical findings in a boy of 13 years who was vaccinated with B.C.G. The Mantoux reaction was negative one week before vaccination and Mantoux conversion developed six weeks later. Eleven months after vaccination he developed tuberculous meningitis; human tubercle bacilli were grown from the cerebrospinal fluid and at necropsy the findings were characteristic of tuberculous meningitis. Rosenthal, Leslie and Loewinsohn (1948) vaccinated a newborn infant with B.C.G. A patch test at the age of 6 months and again at 18 months of age was weakly positive, but at 15 months it was negative. At 22 months of age the infant died from tuberculous meningitis. It is probable that in this patient B.C.G. produced little or no immunity to tuberculosis. Wasz-Höckert (1949) has published observations on twins who were given B.C.G. vaccine three days after birth. In both children Mantoux conversion took place, but in one of them tuberculous meningitis developed six and a half months after vaccination, the diagnosis being confirmed at necropsy. The other twin remained healthy. Savilathi's patient (quoted by Ustvedt, 1951) developed pleurisy six months after successful vaccination with B.C.G. and died from tuberculous meningitis two years later. Lichtenstein (quoted by Ustvedt, 1951) observed an infant who was vaccinated with B.C.G. at birth and in whom the Mantoux reaction became positive but tuberculous meningitis developed two and a half years later. In the Joint Enterprise (Ustvedt, 1951) tuberculous meningitis developed in 16 patients, and miliary tuberculosis in a further five patients, among the 8 million vaccinated. Unfortunately the clinical features of these patients have not been described in detail, but it is clear that at least 10 of the 16 patients

developed tuberculous meningitis within eight weeks of B.C.G. vaccination. Dorothy Price (1954) analysed the results of 140,697 B.C.G. vaccinations performed throughout the Republic of Ireland. Tuberculous disease developed in 21 of these patients but in 11 of them tuberculosis was diagnosed within a few weeks of B.C.G. vaccination and in three patients the diagnosis was not confirmed. One girl of 12 years developed tuberculous meningitis 11 months after successful vaccination and she recovered from the disease. A boy of 6 years became ill 14 months after successful vaccination and died from what was thought to be tuberculous meningitis, but this diagnosis was based on clinical opinion and was not supported by radiological or bacteriological evidence.

The first of the two patients I have described developed tuberculous meningitis seven weeks after B.C.G. vaccination and it seems reasonably certain that he was in the pre-allergic phase of tuberculosis before vaccination was performed. The course of events in the second patient is more difficult to interpret. He was vaccinated on the same day as his brother and six weeks later Mantoux conversion had taken place. He was not in contact with a known case of open pulmonary tuberculosis during this period and he did not present any symptoms even of minor illness. The Mantoux test was performed with a tuberculin solution that was known to be potent, but a second test was not done before vaccination to be sure that he definitely had a negative tuberculin reaction. A radiograph of the chest was not performed at this stage to confirm the absence of pulmonary disease, but a radiograph taken six months later did show an active primary tuberculous complex. It is possible, though unlikely, that he contracted his primary infection from an unknown source at about the same time that B.C.G. vaccine was given, and what was interpreted as Mantoux conversion following B.C.G. was the result of a concurrent primary infection.

It is of interest to compare the response of these two brothers to treatment, contrasted in Figs. 1 and 2, although it could be argued that such a comparison is not valid because of the age difference and the different stage of the disease when treatment was begun. It did seem, however, that response to therapy in the second patient was more rapid than in other patients of the same age, treated at the same stage in their disease, and it is interesting to speculate upon the possible beneficial effects of B.C.G. vaccination on the course of tuberculous meningitis. The following table summarizes the response to treatment in these two patients:

	Patient 1	Patient 2
Clinical response to therapy	Slow	Quick
Temperature	Raised until 16th week	Normal after 12th day
Appetite	Poor for 5 months	Normal throughout
Weight	No gain for first 16 weeks	Steady gain from 1st week
Duration of intrathecal streptomycin	17 weeks	7 weeks
Duration of intramuscular streptomycin	30 weeks	17 weeks
Duration of oral I.N.H.	30 weeks	17 weeks

Summary

The development of tuberculous meningitis in relation to B.C.G. vaccination is a rare event, and the chance of this complication arising, based upon the reported cases, is in the order of 1 in every 400,000 vaccinations. In at least half of these cases meningitis developed while the patients were in the pre-allergic stage of the disease and before vaccination could have any beneficial effect. In a survey of the literature 12 children were found who developed tuberculous meningitis several months after successful B.C.G. vaccination, and a further case is described in this paper. The response of this patient to the accepted treatment for tuberculous meningitis appeared to be more rapid than in patients not vaccinated with B.C.G.

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DOES MEASLES CAUSE HYPERTENSION?

BY

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It is well known that measles seldom affects the circulatory system. Complications appearing under the form of myocarditis are rare (*Year Book of Paediatrics*, 1945). Our special interest, however, was stimulated by the increased blood pressure found during the acute stage of the disease.

In the bibliography available to us we found nothing relating to hypertension in measles, and we feel it is therefore worth while analysing our findings in detail.

The blood pressure of 62 patients, aged between 3 and 13 years, was taken using a mercury manometer with a cuff 7 cm. wide for children below 6 years and 14 cm. wide for the older ones. The values found were compared to those given in the table of Sundal (Catel, 1951).

The blood pressure was considered increased when the systolic pressure was at least 15 mm. above normal and it was appreciably raised in 40, or 60% of the 62 cases. It is well known that accurate estimation of the diastolic pressure is difficult. Fluctuations have been reported depending upon the method of determination (Brock, 1932). We therefore checked the systolic pressure only.

Every possible precaution was taken to ensure the accuracy of our results. Blood pressure was repeatedly determined by several colleagues at the same time. It was also determined in 140 patients of the same age treated in our clinic for disease not causing hypertension and receiving no medication which could influence blood pressure. An increase of over 15 mm. was noted in 30, i.e., in 22·5%. We wish to stress, however, that repeated determinations in many of the above cases proved that hypertension was permanent whereas in measles it was always transitory.

In measles the increase of blood pressure was already present during the catarrhal stage and reached its peak during the eruptive phase. It lasted three to four days and slowly decreased, so that pressure returned to normal values after eight to 10 days.

This hypertension was more evident in children between 3 and 6 years of age, of whom we have had the opportunity to examine a great number.

In Figs. 1 and 2 we give the pressure readings

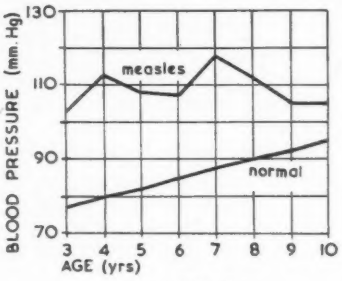

FIG. 1.

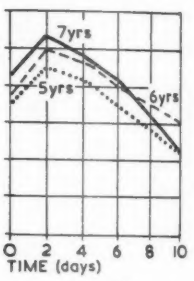

FIG. 2.

according to the age and number of patients. In searching for the probable aetiology (pathogenic mechanism) of this type of hypertension it seemed to us possible to attribute it to endocrine causes, bearing in mind that it is generally accepted today that measles causes oedema and hyperfunction of the adrenal cortex (Macciotta, 1931). Though this explanation is probably the correct one, the participation of other more central factors cannot be excluded. We find a similar example of hypertension for instance in poliomyelitis (Bower, Morgan and Chaney, 1952), where it is believed that the virus stimulates the anterior lobe of the pituitary gland or the reticular cells located in the ventromedial area (Sennet, Perlstein, Andelman, Barnett and Josephy, 1951; Baker, Matzke and Brown, 1950), and through them the adrenal cortex, thus causing hypertension.

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RICKETS WITH ALKALINE PHOSPHATASE DEFICIENCY: AN OSTEOBLASTIC DYSPLASIA

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 10, 1954)

Since the introduction of better diets with ample vitamin supplements by more enlightened mothers, and the virtual disappearance of infantile rickets due to lack of vitamin D, increased interest has been aroused in similar disorders of bone growth from other causes. In studying metabolic, biochemical and renal factors, which can all play a part, our knowledge has become clearer of physiological bone growth, the mechanism whereby calcium and phosphorus are maintained at a constant level in the blood, the part played by enzymes in calcification and of how deviation of these from the normal may be a feature of skeletal disorder.

Recently a girl of 7 months came under our care with hypercalcaemia, renal insufficiency and widespread radiological evidence of 'rachitic' osteoporosis, together with periosteal changes and bizarre bone formation. The diagnosis was very puzzling and no account of similar cases in this country could be found. Investigation showed a serum alkaline phosphatase far below the level associated with an abnormal and improperly calcified matrix. Eventually references were found in the American literature to a rare disorder of skeletal growth in which hypophosphatasia appeared to be a primary factor. Clinically our case seemed to fall into this group, and bone biopsy finally produced additional confirmatory evidence.

Case Reports

Case 1.* C.A., a girl and only child (no miscarriages), was first admitted at the age of 7½ months to the Kent and Canterbury Hospital under the care of Dr. Stanley Rodgers, to whom we are indebted for the early history. Following a normal delivery (birth weight 7 lb. 4 oz.) the baby seemed to thrive for a few weeks, but then began to vomit intermittently and ceased to gain weight regularly. Breast feeding was changed to dried milk at 3 months, when cod liver oil was also introduced, but the symptoms gradually increased until she vomited all her feeds, became restless, then drowsy and so dehydrated that parenteral fluids were required (weight at 7½ months was only 10½ lb.). At no time was there any sign of infection and the stools were normal. Temperature was 100° to 103° F.

One of the most striking features was a widely open, tense, bulging anterior fontanelle, but the cerebrospinal fluid was not under pressure and quite normal. The skull circumference (16½ in.) was not increased. A subdural haematoma was suspected and it was at this stage that she was transferred under our care.

After an *x*-ray examination of the skull it was realized that some gross bone disorder was present. Obvious enlargement of the epiphyseal region of the wrists, knees and ankles, and 'beading' of the costochrondral junctions suggested that the condition was some form of severe rickets, which was supported by further radiographs of the skeleton, although they were not entirely typical. Other clinical findings were rather blue sclerotics, prominent eyes and generalized mild pigmentation.

Radiological Report. Dr. L. G. Blair and Dr. G. N. Weber, reported as follows:

GENERAL. The skeleton was poorly developed for the age (7½ months); there was marked demineralization at the metaphyses and the growing margins of all the bones, producing an irregular, ill-defined margin and in many regions a faintly speckled ghost image of the subepiphyseal region, which was presumably poorly calcified osteoid tissue.

LONG BONES. The mid-shafts were normal. The metaphyses showed an irregular margin, distal to which was a zone of poorly calcified osteoid. In the femur these zones were sharply demarcated, but elsewhere this distinction was less marked. No cupping was present. The epiphyseal lines were irregularly widened. Epiphyseal development was slightly retarded. (Bone age at the wrist was 3 months.)

Epiphyseal calcification was irregular, being less dense centrally in most cases, but the cortex was affected in the same way. Early irregular periosteal new bone formation was seen along the shafts of several bones, particularly the tibiae and humeri (Fig. 1).

* This case was shown to a meeting of the Section of Paediatrics, Royal Society of Medicine, in January, 1954, and a brief description appeared in the *Proc. roy. Soc. Med.*, 1954, **47**, 541.

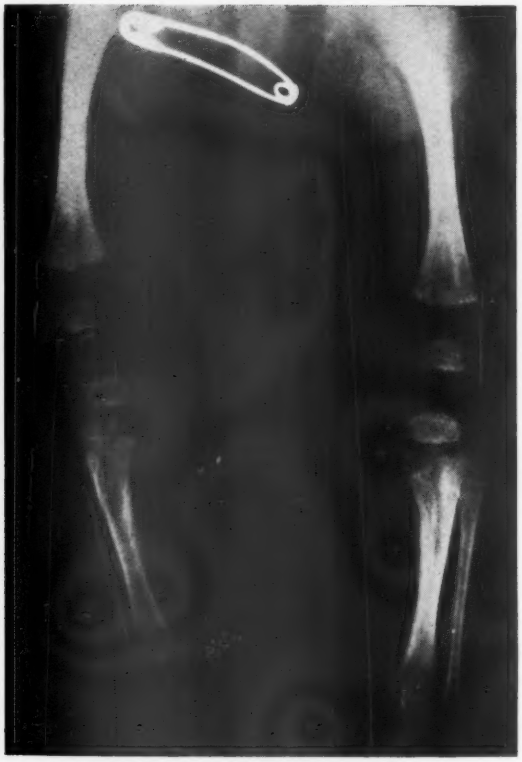

FIG. 1.—Radiograph of the lower limbs of Case 1 at the age of 7½ months, showing irregular calcification of the metaphyses and epiphyses, zones of poorly calcified osteoid at the lower ends of the femora and early periosteal new bone formation along the shafts.

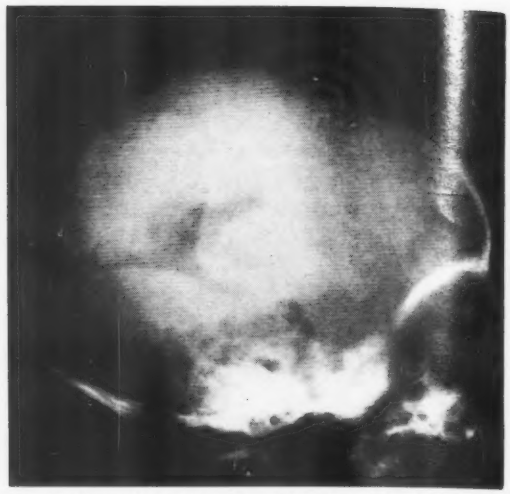

FIG. 2.—Radiograph (ventriculograph) of the skull of Case 1 at the age of 8 months, showing widened sutures, a bulging anterior fontanelle and defective ossification.

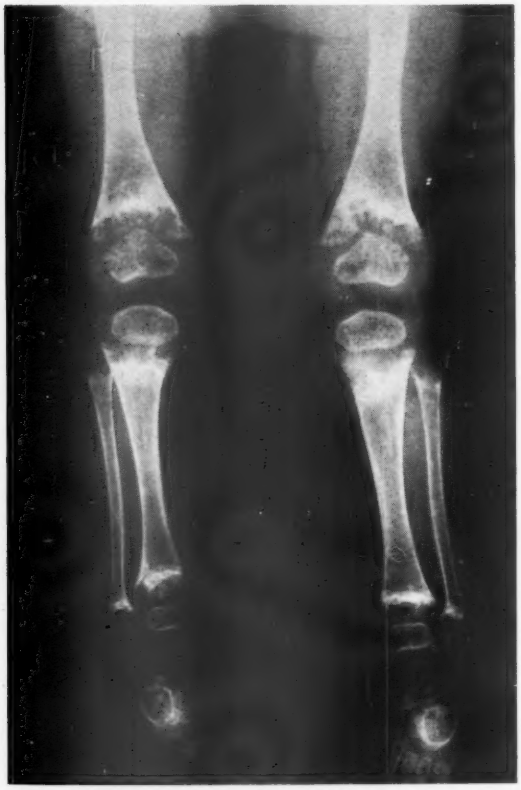

FIG. 3.—Radiograph of the lower limbs of Case 1 at 11 months, showing improved but still disordered ossification with cupping of the bone ends

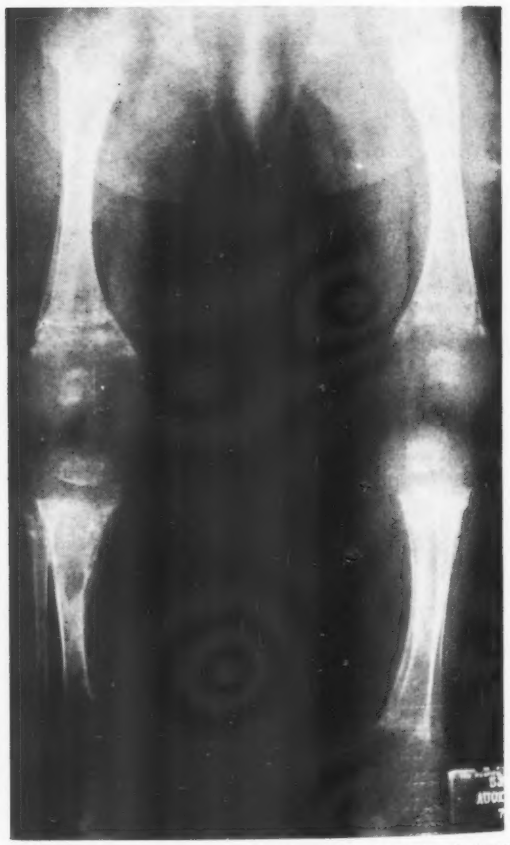

FIG. 4—Increasing but irregular calcification in Case 1 at just over 1 year of age, with striking periosteal new bone formation along the shafts.

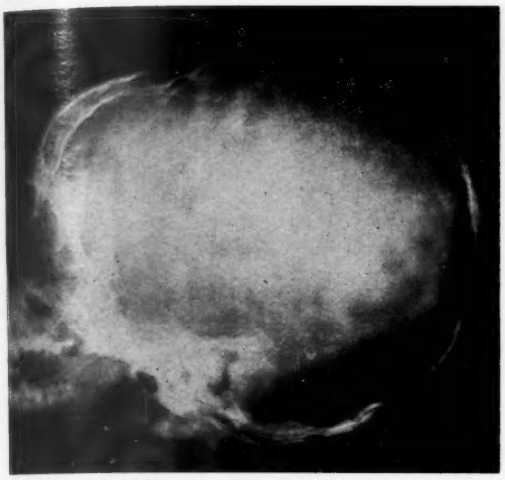

FIG. 5.—The skull of Case 1 at 20 months is now well calcified, but there is premature closure of the sutures, producing abnormal growth of the vault.

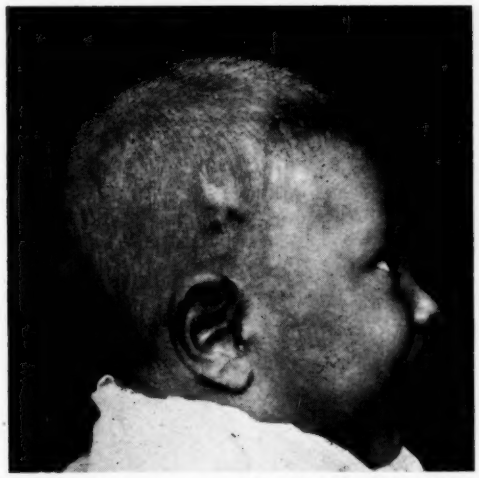

FIG. 7.—The curious appearance of Case 1 at 14 months with deformity of the skull as a result of craniostenosis.

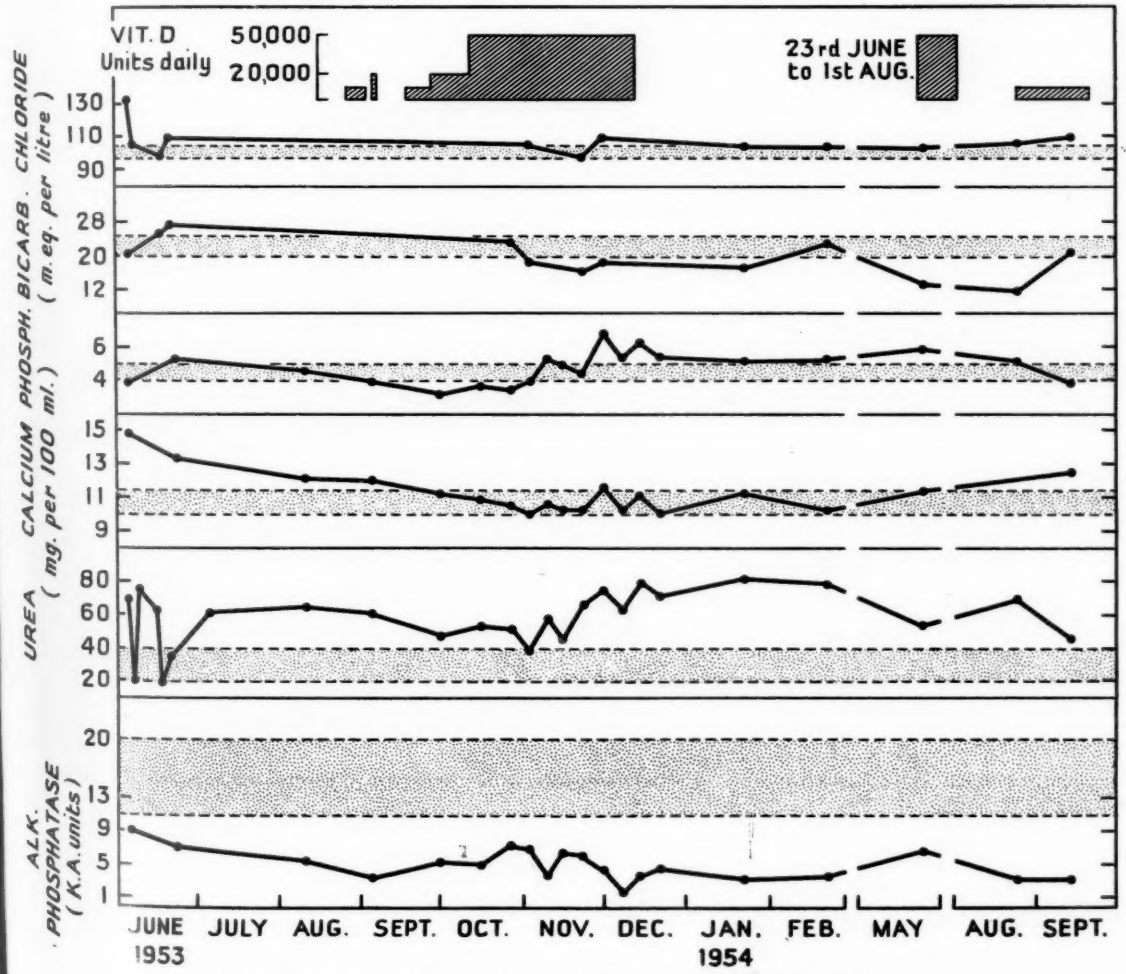

FIG. 6.—Diagram of the serological investigations over a period of 11 months.

Ribs. The rib ends, which were demineralized and ill defined, were slightly expanded.

Skull. There was defective ossification throughout, resulting in widening of the sutures at the base and vault, and irregular growing margins of the flat bones. Scattered flecks of calcification in the suture lines were presumably attempts at ossification in the osteoid tissue. There was slight bulging of the enlarged anterior fontanelle (Fig. 2).

Pelvis, Scapulae, Spine. Similar changes with fluffy bone margins and patchy mineralization were present throughout.

During the months of June, July and August, 1953, slowly increasing changes of patchy demineralization appeared at the bone ends, with extension of the periosteal thickening to most of the long bones. The epiphyses became less dense and one or two of the carpal centres had almost completely disappeared.

By September mineralization was improving throughout (Fig. 3). Periosteal thickening in the long bones and ribs had increased and ossification at the sutures had improved. The skull had a curious shape with bulging of the vertex and deficient growth of the frontal region, as the coronal and squamosal sutures were beginning to close.

In October there was further improvement (Fig. 4). There was now well-marked cupping of the bone ends, well seen in the knees and ribs.

On May 24, 1954, when the child was 20 months old, development was still retarded and there was considerable general porosis. The subperiosteal new bone was now consolidating. The metaphyses remained cupped and markedly irregular. Epiphyseal development was slightly retarded. (The bone age at the wrist was 15 months.)

The skull was well calcified; the anterior fontanelle and coronal and squamosal sutures had prematurely closed, causing restricted growth of the vault anteriorly and a prominence at the vertex (Fig. 5).

A trephine hole had been made in the right parietal region in the treatment of subdural haematoma on June 17, 1953. This measured 17 mm. across on films dated June 26, 1953, and had progressively increased in size to 23 mm. on the films of May 24, 1954. This is a reversal of the usual slow disappearance of a trephine hole.

Serological Investigations. These, over a period of 11 months, are presented in Fig. 6. The chief findings were a low serum alkaline phosphatase level, a raised serum calcium level falling to normal later, a low serum phosphorus level with a subsequent rise to normal and a persistently high blood urea concentration, with a normal cholesterol level. The serum protein was normal in total and albumin/globulin ratio, and electrophoresis produced a standard pattern. The acid-base balance was normal except for brief periods of acidosis. The blood Wassermann, P.P.R. and Kahn tests and the cerebrospinal fluid Wassermann reaction were negative.

Blood Counts. Blood counts revealed a severe normochromic anaemia (50% Hb) soon after admission to hospital, necessitating a blood transfusion; thereafter there was a moderate anaemia (70% Hb), from which the infant eventually recovered. An initial leucocytosis (17,600 W.B.C. per c.mm.) with a normal differential count was present, but before long this disappeared.

Urine. Most specimens of urine contained some pus cells and a trace of albumin; usually they were sterile, but at times a light growth of *Bact. coli* was obtained. The reaction was on the whole acid; amino-aciduria and glycosuria were absent. Urea clearance at the age of 1 year in two successive specimens was 40·9% (standard clearance) and 56·2% (maximum clearance), which, together with the constantly raised blood urea and poor excretion of dye on pyelography, indicated renal impairment. There were no retinal changes at this period.

The urine was again examined by Dr. Charles Dent 22 months later, and he reported as follows:

'The standard chromatogram showed a rather weaker pattern than for the previous urine examined on January 25, 1953, as if to suggest that there was an increase in renal damage since that date. As far as we could see from this, however, the pattern was normal. In view of our findings with the urine from McCance's case we have done a further chromatogram, over-loaded five times, so as to show the weaker spots more easily. This now makes it quite clear that there is a definite abnormality in this urine, for the over-loaded chromatogram showed a good spot corresponding to ethanolamine phosphate, not very strong but nevertheless quite pathological. It is possible that this was present in the previous urine but was not detected as we only did a normal chromatogram.'

A positive calcium and phosphorus balance was demonstrated by Dr. Payne and Dr. Wilkinson (Table I),

TABLE 1

CALCIUM AND PHOSPHORUS BALANCE

Period = 3 days Calcium ( ) = daily mg.	Phosphorus ( ) = daily mg.
Intake (by analysis)	
Feeds 3,486 mg. (1,162)	3,087 mg. (1,029)
Rejects 439 mg.	455 mg.
3,047 mg. (1,016)	2,632 mg. (877)
Output	
Faeces 2,026 mg. (675)	1,145 mg. (381)
Urine 268 mg. (89)	1,064 mg. (355)
2,294 mg. (764)	2,209 mg. (736)
Balance	
Calcium + 753 mg. (251)	Phosphorus + 423 mg. (141)

and the Sulkowitch test showed a normal precipitate, except after a three-month course of vitamin D in high dosage, when for a time there was evidence of excessive urinary calcium excretion, which soon reverted to normal when this treatment was stopped. It was at this time too that the only high blood inorganic phosphorus readings were obtained (6·7 and 6·2 mg. %), presumably due to renal insufficiency.

The early clinical picture was further complicated by the actual presence of a right-sided subdural haematoma. This diagnosis had been suspected originally, but rejected in view of a negative subdural tap and of all the other

FIG. 8.—Photomicrograph of biopsy from tibia on August 12, 1953 (× 60, haematoxylin and eosin stain) to show the abnormal organic matrix at the margins of the bone trabeculae and the paucity of osteoblasts.

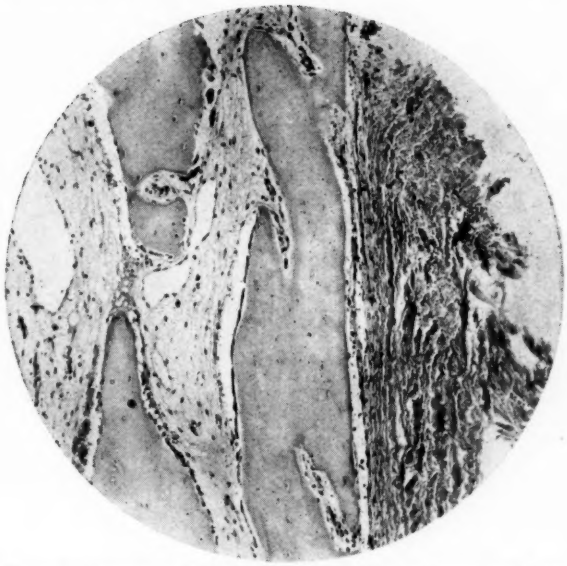

FIG. 9.—Photomicrograph of biopsy from tibia on December 2, 1953 (× 60 haematoxylin and eosin stain) to show the bone trabeculae and the osteoblasts approaching normal. The seams of abnormal matrix have disappeared.

findings. When, however, left-sided fits suddenly arose, and a ventriculogram showed some displacement of the ventricular system, craniotomy was performed and a thin film of black blood clot was removed. It became clear nevertheless that the bulging fontanelle, which remained, had no connexion with this complication.

During the following six months of the child's stay in hospital progress was slow; she vomited at least one feed almost daily, anorexia was marked and gain in weight accordingly unsteady. Radiological examination failed to demonstrate any oesophageal lesion or delay in gastric emptying. The skull circumference showed little increase in size and at 14 months it still remained 17½ in., growth taking place largely in a vertical direction in the posterior region, giving the child an oxycephalic appearance, further enhanced by rather prominent eyes (Fig. 7). The anterior fontanelle continued to bulge until it eventually closed at 16 months, and the same tenseness of the burr hole has continued throughout.

After the infant had been in hospital for three months it was decided to try the effect of vitamin D in high dosage, 10,000 units rising to 50,000 units daily. Improvement in her general condition appeared to coincide with this course; she became happier and more lively, a slightly better appetite developed, the vomiting eventually ceased and there was a steady gain in weight. At the same time the serum calcium fell to normal and calcification of the bones began to be more satisfactory. The treatment was stopped after about three months, as the serum calcium level showed signs of rising again and the serum phosphorus level was also noticed to be higher than normal.

The child has been examined periodically during the last year and has progressed slowly, but epiphyseal enlargement is still marked at the wrists and ankles, and a 'rosary' is palpable at the costochondral junctions. Although she has now reached the age of 2 years, she cannot stand or bear any weight on her legs. On the other hand she has begun to talk, and she is an exceptionally bright and amiable little girl with fair intelligence. The blood pressure appears to be high, between 120 and 140 mm. Hg (systolic), and the blood urea level remains raised but is tending to fall towards normal (last record, 46 mg. per 100 ml.). For the last year the blood calcium level has been normal, but it rose again to 12·6 mg. per 100 ml. after a further course of vitamin D in high dosage (Fig. 6), when an increased excretion of calcium in the urine was also discovered. A low blood phosphatase level has persisted throughout. Radiological progress of bone growth has already been recorded.

Recently the child was again admitted to hospital for reassessment. Her general condition was good, but it was obvious from the increasing tension at the site of the old burr hole and the curious shape of the skull that craniostenosis had developed to a dangerous degree. The appearance of papilloedema confirmed this fear and a linear coronal craniotomy was successfully performed to relieve the increased intracranial pressure.

Meanwhile the mother was approaching term in her second pregnancy, but no radiological evidence of a similar bone disorder was found in the foetus.*

Final proof of lack of phosphatase was found at a bone biopsy, carried out on three occasions.

Bone Biopsy. The composite histological report of three biopsies of bone taken from the skull at 8 months and the upper end of right tibia at 10 and 14 months is as follows:

The first two biopsies from skull and right tibia, respectively, showed comparable features. The trabe-

* Post-natal progress is reported under 'Heredity' p. 275.

culae consisted of a slender central core of lamellar and woven bone and a conspicuous marginal zone of partially calcified connective tissue matrix, without any of the orderly architecture of osteoid seams. There was paucity of osteoblasts and osteoclasts at the margins of the trabeculae, and osteocytes too were only moderately well represented. The marrow showed no fibrosis (Fig. 8).

The third biopsy showed a greater approach to normal bone. The abnormal calcified connective tissue matrix had disappeared, the bone trabeculae were wider and rows of osteoblasts flanked the margins of the trabeculae. The uneven staining of the newly formed bone and the smaller size and number of osteoblasts were still somewhat abnormal features (Fig. 9).

Quantitative analysis of bone phosphatase was carried out by Dr. W. W. Payne and Dr. R. H. Wilkinson (Table 2).

TABLE 2

QUANTITATIVE ESTIMATION OF BONE PHOSPHATASE*

Case 1 (C.A.)	Normal Control (Necropsy)
Tibial cortex (quenched at -40° C.) 150 N.P.P. units/kg./ wet tissue	530 N.P.P. units/kg./wet tissue
Calvarium	560 N.P.P. units/kg./ wet tissue
Tibial periosteum 150 N.P.P. units/kg./wet tissue	

* Method of Bessey, Lowry and Brock (1946). *J. biol. Chem.*, **164**, 321.

Histochemical preparations and biochemical estimations suggested a reduction in phosphatase activity in the excised bone and periosteum.

The changes observed indicated a defect in the process of ossification (dysostosis), manifesting itself in the production of an abnormal organic matrix and in quantitative and qualitative deficiency of osteoblasts.

The mother and father were investigated but no similar deficiency was found.

	Serum Calcium (mg. %)	Serum Phosphorus (mg. %)	Alkaline Phosphatase (King-Armstrong units)
Mr. A. ..	10·4	3·8	5·7
Mrs. A. ..	9·9	1·9	5·6

About this time another case came to our notice under the care of Dr. R. L. Langley, to whom we are indebted for allowing us to include it in this report.

Case 2. S.H., a girl (birth weight 8 lb. 9 oz.), the first child of young healthy parents was brought to hospital at the age of 6 months because of vomiting and failure to thrive (weight at 6 months, 12 lb. 6 oz.). The infant had been breast fed with National dried milk complements until the age of 3 months, when she was weaned on to full-cream National dried milk, subsequently changed to Cow and Gate full-cream dried milk without any improvement in the vomiting, which was irregular and never immediately after feeds. Cod liver oil had been offered but refused, and no other vitamin D supplement was given except the standard amount contained in the dried milk.

On examination, enlargement of the epiphyseal end of the forearms and the costochondral junctions suggested at once the presence of rickets. There was marked dorsal kyphoscoliosis and a tendency to calcaneo valgus. In addition certain other puzzling features were noticed. The anterior fontanelle was not only widely patent but was also remarkably tense (skull circumference 17 in. at 6 months). Since there was also unexplained fever for the first two weeks in hospital, ranging between 101° and 104° F., meningitis was suspected, but repeated lumbar punctures yielded a normal cerebrospinal fluid. The pyrexia did not respond to penicillin but appeared to subside fairly rapidly after chloramphenicol. Restlessness with a continual rotary movement of the hands and feet was another curious symptom. The radiological changes in the bones resembled closely those seen in Case 1.

Radiological Report. Dr. R. L. Hill reported as follows:

GENERAL. The skull showed defective ossification in

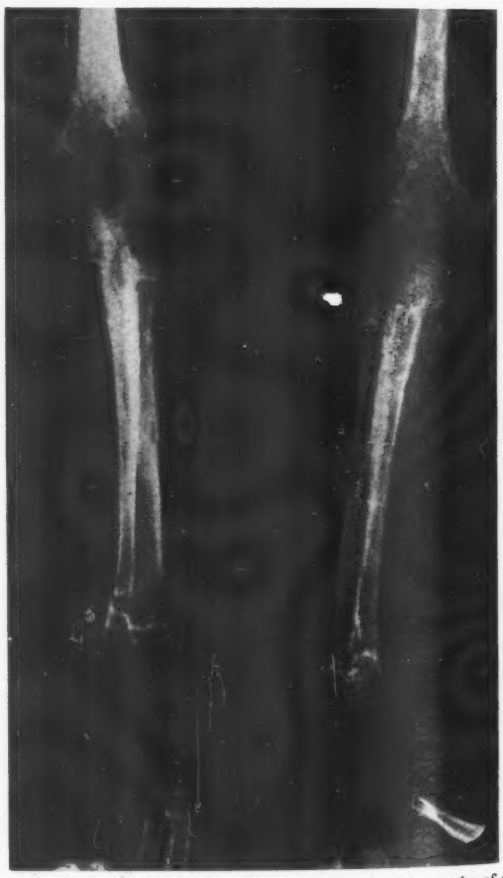

FIG. 10.—Radiograph of upper limbs of Case 2 at 6 months of age, showing the same ossification defects and deposition of periosteal new bone. Osteoporotic fractures are visible at the lower ends of both ulnae.

the base and vault. There were extensive bony changes throughout the skeleton, with profound disturbance of ossification in the metaphyses of the long bones and pelvis (Fig. 10). The ribs showed periosteal new bone. The metacarpals appeared normal. The appearances suggested a chondro-osteodystrophy with superadded rachitic changes.

SKULL. On June 12, 1953, when the baby was 8 months old, there was still defective ossification of the cranial vault, but considerable improvement since the previous examination.

LONG BONES. Marked improvement in bone detail was also seen at the left elbow, with ossification in the osteoid tissue in the metaphyses. The same could be said of the left knee, and the general picture was that of healing rickets.

SKULL. On two occasions in July, 1953, when the baby was 9 months old, advancing calcification of the bones of the cranial vault was visible. There was, however, a generalized increase in the convolutional markings.

LONG BONES. In the long bones improvement at the left elbow continued and the bones were approaching normality.

In October of the same year improvement in ossification was maintained. The anterior fontanelle was still very wide and the lacunar pattern in the skull persisted.

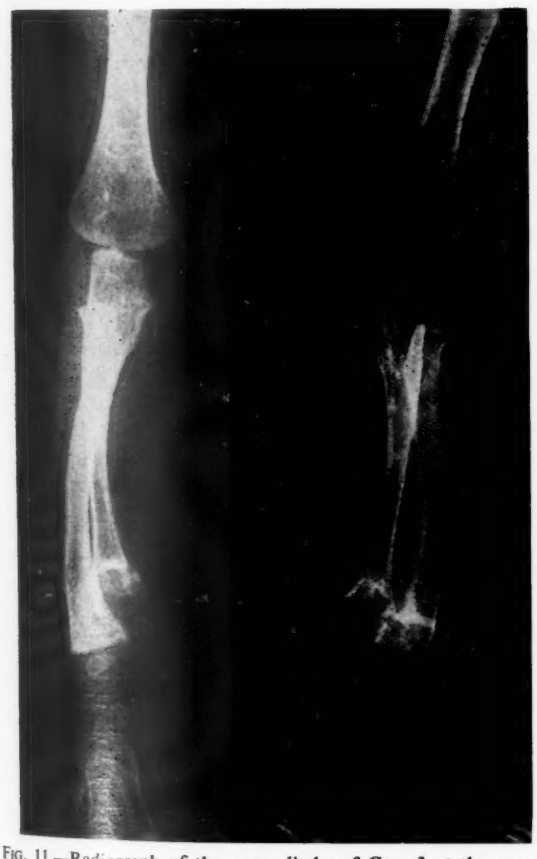

FIG. 11.—Radiograph of the upper limbs of Case 3 at the age of 2 years, showing a wide zone of poorly mineralized osteoid and slight periosteal reaction over the shafts.

LONG BONES. On February 10, 1954, when the child was aged 15 months, there was further improvement; the bones of the upper limbs were now normal and those of the lower limbs were nearly so.

SKULL. The cranial vault had ossified further, but there was still a bulge in the region of the anterior fontanelle and increased lacunar markings. The base remained rather short and steep and there was a linear plaque of calcification in the suprasellar region.

On August 23, 1954, the child now being 21 months old, the appearance of the long bones was normal except at the lower femoral metaphyses, where there were well defined, elongated, translucent areas extending up the femoral shafts. The vault of the skull was asymmetrical, with relative flattening of the frontal and left parietal regions, where the convolutional markings were still prominent. There appeared to be partial fusion of the coronal sutures.

Serological Investigations. These gave the following results: a normal serum calcium level, 10·8 mg. per 100 ml., and blood inorganic phosphorus level, 4·8 mg. per 100 ml. The serum alkaline phosphatase, 7·3 King-Armstrong units per 100 ml., was low, considering the deficient calcification of the bones. Wassermann reactions of both parents and the child were negative. The urine was normal; there was no anaemia and the total and differential white cell counts were normal. During the infant's stay in hospital she had two infections, tonsillitis with otitis media and a right lower lobe pneumonia, which responded well to aureomycin.

Treatment adopted was 'radiostoleum' in moderately high dosage, 30 minims daily. On this regime progress was maintained, appetite improved on a mixed diet and a steady gain in weight was achieved (14 lb. at the age of 9 months). There was also radiological evidence of improved ossification. For a time the 'radiostoleum' was dropped to 20 minims daily. Within a fortnight clinical deterioration was noticed; general irritability with purposeless movement of the hands recurred and the baby was reluctant to sit up. When the original dose of vitamin D was resumed, these symptoms rapidly disappeared. Meanwhile, the anterior fontanelle was gradually becoming smaller, although it still felt rather tense, and the surrounding bones of the skull were raised and the area was rather like the crater of a volcano. At the age of 14 months the fontanelle was closed, the baby was sitting up well, trying to stand and the mentality was normal.

The child is now nearly 2 years old and her general condition is excellent; the blood urea is 28 mg. per 100 ml., serum phosphorus, 3·7 mg. per 100 ml., blood calcium, 10·7 mg. per 100 ml., but the serum alkaline phosphatase level remains low, 3 King-Armstrong units per 100 ml. Radiological progress of ossification has already been recorded in the series of *x*-ray reports.

A third case has since been brought to our notice by Sir Thomas Fairbank. She is under the care of Mr. J. S. Maxwell, and we are grateful to him for allowing us to include the case here.

Case 3. M.M. was a girl, aged 2½ years. At the age of 2 years the parents first noticed that the legs were weak, and that she had knock knees. It had become worse when she began to walk at about this time. On examination the child was heavy, had a large globular head, poorly developed lower limbs and gross symmetrical genu valgum. She walked with difficulty and had a rolling gait. At the age of 2 years the serum calcium was raised to 12·1 mg. per 100 ml. and the serum phosphatase was low, 2·4 King-Armstrong units per 100 ml., and a month later 6·3 units, with a blood urea of 64 mg. per 100 ml. The Wassermann and Kahn reactions were negative. The urine was normal except for evidence of increased calcium excretion (Sulkowitch).

Radiological Report. The *x*-ray appearances were as follows:

LONG BONES. On September 15, 1953, when the child was 2 years 1 month old, slight general demineralization was present. The metaphyses showed a wide zone of poorly mineralized osteoid, fairly well-demarcated from the normal looking shaft by an irregular line of sclerosis. Slight cupping was visible with some periosteal reaction over the shafts of fibulae and ulnae. The epiphyses were poorly but evenly mineralized. Bone age was within the normal limits (Fig. 11).

SKULL. The vault was large and slightly thinned, with marked increase in convolutional markings throughout. The pituitary fossa was normal. A small prominence was present at the bregma. All vault sutures appeared fused (Fig. 12).

RIBS AND CHEST. On January 12, 1954, the child, now aged 2 years 5 months, the anterior ends of the ribs were poorly mineralized, ill defined and slightly cupped. Irregular mineralization of osteoid was seen at the growing points in the upper humeri and scapulae.

LONG BONES. By June 22, 1954, when the child was 2 years 10 months old, considerable growth had occurred at the bone ends. The metaphyses were better mineralized, but deep zones of irregular ossification remained. There was still slight cupping at several of the metaphyses and also bilateral genu valgum deformity due to asymmetrical growth.

Bone age had not appreciably advanced since September 15, 1953.

SPINE AND PELVIS. The bone texture was mottled and the growing margins were fluffy at several points. The anterior ends of the ribs were slightly expanded and more cupped than previously, but now clearly defined.

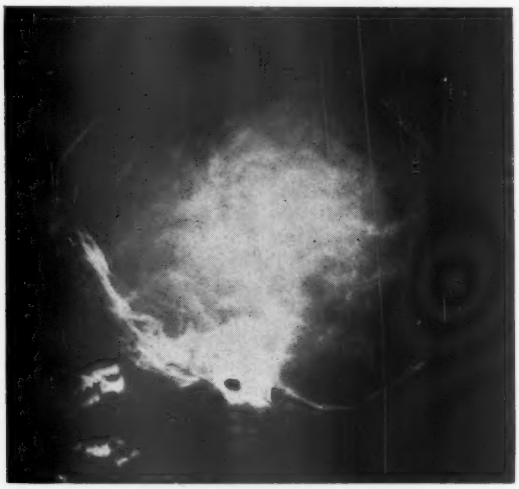

FIG. 12.—Radiograph of the skull of Case 3 at 2 years of age, showing a thin vault with increased convolutional markings and fused sutures throughout.

The child's teeth are quite normal and she is above average in intelligence. Walking continues to be difficult. For the last eight months she has been on 50,000 units of vitamin D daily. There is one older brother aged 8 years, who is healthy and whose bones appear normal radiologically. His serum alkaline phosphatase level of 12·6 units per 100 ml. is normal. No other member of the family has suffered from any bone disease.

Two of these three cases are strikingly similar in the early onset of vomiting, their failure to thrive and anorexia, the clinical and radiological appearance of the bones, tense fontanelle and low alkaline phosphatase of the blood. Case 1 was apparently the severer of the two and was complicated by hypercalcaemia and renal damage. Case 2 improved fairly rapidly, and both clinically and radiologically was approaching normal when last examined. Case 1, on the other hand, still has radiological evidence of defective bone growth; the blood urea level remains high, although the serum calcium has dropped to normal apart from a fresh rise recently after further vitamin D therapy. Case 3 had no generalized symptoms during infancy, despite the slight rise of serum calcium recorded later, which seemed to be sufficient to cause some impairment of renal function. It was an orthopaedic disability that brought her to the doctor. She has shown some improvement, but bone growth has not yet become normal.

Fusion of the skull sutures and craniostenosis are a feature in all three and a persistent low alkaline phosphatase level appears to be a common defect.

Review of the Literature

Occasional reports of a disorder like the one described have appeared in the American medical journals. Rathbun (1948) first directed attention to an osteodystrophic condition in which serum alkaline phosphatase was deficient. This he found in a male infant of 3 weeks who died at the age of 1 year. Deformities of the wrists, bowing of the legs and beading of the costochondral junctions were present. The skull bones consisted merely of four rounded plaques in the frontal and parietal areas, and the remainder of the vault 'felt like a balloon filled with

water'. Serum calcium was raised at first (13·6 mg. per 100 ml.), later falling to a normal level, while the serum phosphorus remained high throughout (6·9 to 5·2 to 10·5 mg. per 100 ml.). The serum alkaline phosphatase was exceptionally low (0·0 to 0·7 Lowry-Bessey units or 0·0 to 5·1 King-Armstrong units), and at necropsy many tissues were found to have a greatly reduced alkaline phosphatase content as well. *X*-ray examination during life showed marked lack of calcification of the skull and vertebrae, and ossification defects with 'flaring' at the costochondral junctions and at the metaphyseal ends of the long bones. Fractures were also seen in the radius and ulna. Anaemia was present, necessitating a transfusion. Various forms of treatment were tried without avail, including vitamin D supplements, and the infant died after a series of convulsions.

The main findings at necropsy were tubular lesions in the kidneys with no evidence of calcinosis, suggesting a low-grade inflammatory reaction. Changes in the long bones resembled severe rickets. In the skull the framework appeared to be normally laid down in the form of osteoid tissue, periosteum, osteocytes, osteoblasts and organic intercellular material, but lacked calcification except in the four plaques previously mentioned.

Schneider and Corcoran (1950) described two brothers, aged 10 and 13 years, with bilateral genu valgum. Radiographs revealed increased density of the metaphyses with areas of rarefaction, irregular epiphyseal lines in the long bones and rarefaction in the scapulae. The serum calcium was raised and serum alkaline phosphatase less than 1 Bodansky unit (4 King-Armstrong units) in both patients. Both parents had low serum alkaline phosphatase levels.

Sobel, Clark, Fox and Robinow (1953) reported a further case, a girl of 19 months, who showed clinical and radiological evidence of rickets, premature loss of milk teeth and irregular calcification of the permanent teeth. The serum calcium and phosphorus levels were normal, but here again the serum alkaline phosphatase was abnormally low, 0·8 to 1·64 Lowry-Bessey units (5·8 to 11·97 King-Armstrong units). Biopsy of the liver and a rib also showed an alkaline phosphatase content far below normal. The father of this patient had a low serum alkaline phosphatase level, and two of the child's near relations had skeletal abnormalities described as dyschondroplasia.

The most hopeful line of treatment in this case seemed to have been high vitamin D dosage. This produced some improvement in bone calcification and a temporary rise of serum alkaline phosphatase to three times its former level, although it still remained abnormally low. Nevertheless the treatment had to be abandoned when signs of calcium intoxication appeared—anorexia and vomiting—and the serum calcium rose to 17 mg. per 100 ml. Renal function was not impaired. General progress was reported as satisfactory, but the skeletal disorder continued.

The authors mention five other cases, including two siblings who died with the same disorder; in four, one or both parents had low serum alkaline phosphatase levels.

Other probable examples of this disease should be added. Anspach and Clifton (1939) published a case which they regarded as hyperparathyroidism. This was a girl of 4 years who at 3 months was suffering from anorexia, failure to gain weight, polyuria, tender limbs and swelling near the joints. The skull felt soft in the occipital region; the anterior fontanelle bulged markedly without other signs of increased intracranial pressure. At 9 months the sagittal suture became elevated into a ridge. The radiological changes were 'cupping' at the metaphyseal ends of the long bones, with imperfect ossification and a thin cortex. The bony tables of the skull were thin; digitations and many fracture lines were present.

The serum calcium was raised to 16·2-14·5 mg. per 100 ml., the phosphorus was low, 2·3-3·7 mg. per 100 ml., and the serum alkaline phosphatase was 12 units, falling later to 2 Bodansky units (8 King-Armstrong units). At 2 years the condition had deteriorated; the child only weighed 15 lb.; there was hypotonia, prominence of scalp veins and some proptosis. The head felt soft and nodular, the fontanelle was bluntly cone-shaped and calcification of the skull and long bones was grossly deficient. Renal function was not greatly impaired, although the blood urea was slightly raised (48·9 mg. per 100 ml.) and the blood cholesterol level was high (243 mg. per 100 ml.).

By the age of 4 years there was marked physical improvement, except for blindness which had developed, and the bones had almost completely become recalcified. The serum calcium and phosphorus had both reached a normal level but the alkaline phosphatase was still low, 1·5 Bodansky units (6 King-Armstrong units). The authors believed they had cured the condition by *x*-ray irradiation over the parathyroid region, but this seems very doubtful, and as operation had been refused, hyperparathyroidism was never established.

Chown (1936) described a case which he labelled 'renal rickets and dwarfism', in which the pituitary gland was thought to be implicated. Hypercalcaemia was present, but no mention is made

of the level of alkaline phosphatase. Radiologically all the bones of the skeleton showed evidence in varying degree of imperfect calcification, similar to the condition we are considering, and it may well have been another example.

The most recent reference to this disease is by Engfeldt and Zetterström (1954), who describe a fatal case at 10 months of age with marked renal impairment. She was the second child of healthy parents with no relevant family history. She was given 1,000 units of vitamin D from birth and progressed satisfactorily to the age of 3 months. At this stage anorexia and vomiting started, she became hypotonic and ceased to gain weight. At the age of 5 months she was found to have a skeletal disease resembling rickets with maximal involvement of the skull. Her systolic blood pressure was elevated. Investigations showed a reduced urinary concentration, a raised non-protein nitrogen level, mild hypercalcaemia and a lowered serum alkaline phosphatase. At 9 months a marked thoraco-lumbar kyphosis appeared.

There were repeated upper respiratory infections and at 10 months she died of pulmonary and cardiac failure.

The findings at necropsy were of a generalized retardation of growth of the skeleton, with inhibition of the remodelling of bone. There was abundant formation of an abnormal osteoid matrix and osteoblasts and osteoclasts were reduced in number. Alkaline phosphatase activity of the bone was low. There was also nephrocalcinosis with fibrosis.

Discussion

A fairly clear-cut syndrome emerges from a study of our three cases, comprising severe skeletal dysplasia associated with a low serum alkaline phosphatase. Hypercalcaemia is commonly present with a positive calcium and phosphorus balance. There may be impairment of renal function. Vomiting, anorexia, and failure to gain weight are the main features and sometimes fever, symptoms no doubt of the hypercalcaemia. Rickets is often suspected at first, but the early age of onset, the tense bulging fontanelle, atypical radiological changes, peculiar histological pattern and, above all, the low alkaline phosphatase level cannot be reconciled with this diagnosis. A hereditary factor seems to be present in some of the reported cases. The disorder can be expected to take a favourable course in most instances. Eventually bone calcifies, symptoms abate, and blood calcium and phosphorus levels return to normal. On the other hand, the serum alkaline phosphatase level remains low and there appears to be no guarantee that the kidneys will fully recover from any damage they may have sustained. A fatal prognosis is usually associated with extremely low levels of serum alkaline phosphatase, hypercalcaemia with resulting severe renal damage and an advanced state of the disorder early in infancy. The condition has, in fact, been diagnosed radiologically before birth, when a previous sibling has had the disease and died from its effects. (McCance and Fairweather, 1954.) Early craniostenosis may also prove a real danger to sight.

In the differential diagnosis several disorders have to be considered which bear some resemblance to the condition we are discussing, although they show striking differences in their clinical behaviour and their biochemical, radiological and histological abnormalities. Somewhat similar bone lesions with periostitis are seen in congenital syphilis, but serological tests for this infection have been consistently negative. Hyperparathyroidism is a diagnosis readily advanced whenever some peculiar rarifying bone disease is associated with hypercalcaemia, but a high rather than a low serum alkaline phosphatase level would almost certainly be present, and there would also be evidence of increased phosphorus excretion in the urine.

The radiological appearances of dyschondroplasia (Ollier's disease) is hardly comparable and metaphyseal dysostosis is not associated with a low plasma phosphatase, though hypercalcaemia is present. The same can be said of leukaemia and myelomatosis, which in any case can be readily excluded by marrow puncture.

There are not many disorders in which the serum alkaline phosphatase level is reduced. It has been reported in scurvy (Smith, 1933; Schwachman, 1941), hypothyroidism (Talbot, Hoeffel, Shwachman and Tuohy, 1941) and rarely in achondroplasia, osteogenesis imperfecta (Hansen, 1934) and severe malnutrition (Talbot *et al.*, 1941). In all these conditions the deficiency is moderate, and in scurvy and hypothyroidism is rapidly overcome with appropriate treatment. Much lower levels are found in the syndrome we are describing and the deficiency may almost be complete as in Rathbun's case. No treatment has been found capable of reversing this apparent congenital defect.

Phosphatase and Ossification. The exact role played by alkaline phosphatase in bone formation is still uncertain, but there is little doubt that adequate amounts are essential to ensure normal skeletal development. Recent evidence suggests that phosphatase is more concerned with the production and maturation of the protein matrix of osseous tissue than with the precipitation or crystallization of bone salts in it (Bourne, 1943a and b, 1948; Siffert, 1951;

Pritchard, 1952). In mature bone phosphatase is found in the endosteum and in the inner layer of the periosteum. It is present in the superficial, osteocytes and in recently deposited bone matrix, but disappears from these regions as they grow older. The mesenchyme destined to form membranous bone in the developing embryo also contains phosphatase, but it only appears in cartilage just before ossification, first in the nuclei and then spreading to the cytoplasm and the matrix. Periosteal osteoblasts appear to go through a cycle of phosphatase activity in growing bone, which they retain when they become young osteocytes surrounded by bone matrix. As they become older they lose their phosphatase, but under certain circumstances, particularly in bone injuries and repair, they may show signs of renewed activity. Osteoclasts also contain phosphatase (Bourne, 1954).

The histology in Case 1 of the skeletal disorder we are now describing demonstrated a markedly defective bone matrix, which was represented by a disorderly architecture of fibrous tissue, few osteoblasts at the margins of the bone trabeculae and amorphous calcification. The histological features suggested a primary defect in the production of osteoblasts, with a resulting lack of sufficient phosphatase, which in turn prevented the formation of a proper template and matrix in which normal ossification could proceed. This theory appears to fit in best with the modern view of bone growth which has just been described.

Further evidence was provided by the behaviour of the trephine hole in the parietal region of the skull. Normal repair in this region depends on an adequate production of phosphatase, which first appears with large numbers of polymorphs and fibroblasts, and later in association with osteoblastic activity and the formation of calcified osteoid. In our case there was little sign of healing 14 months after the operation, and radiologically, in fact, the diameter of the burr hole had increased with growth of the skull.

Heredity. In the three cases we have studied the parents were healthy and in one (C.A.), where tests were possible, there was no suggestion of hypophosphatasaemia in either the mother or father. All three were first children and C.A.'s unborn sibling appeared to have normal bone development on radiological examination. After birth, at 6 weeks of age, a radiograph of the long bones was normal, but the serum alkaline phosphatase was at the low level of 4·5 to 7·6 units per 100 ml., and Dr. Dent was able to demonstrate the same abnormal amino-acid, ethanolamine phosphate, in the urine as in the affected sister. Serum calcium was 11·2 mg. per 100 ml.

The literature contains several accounts of the same disorder in other close members of the family, or a familial trait with low phosphatase blood levels (Schneider and Corcoran, 1950; Sobel *et al.*, 1953). Premature loss of teeth has been noted in some, but this was not a feature in our cases. No definite conclusions can yet be drawn on the genetics of the disorder.

There is no evidence of any teratogenic influences, either in the form of an infection, the action of a toxic agent or vitamin deficiency in the mother during pregnancy.

Radiology. The main defect appears to be abnormal patchy calcification at the metaphyses and growing edges of the bones, producing an irregular, ill-defined margin. This varies in degree; in some the whole skeleton is involved, in others certain regions which are not the growing points escape, as for example the upper end of the femur in Case 3. In the long bones the metaphyses are more severely involved than the epiphyses, but here as well calcification is abnormal. Bowing may be present and the rib ends are expanded, demineralized and ill defined. The periosteum is elevated due to early irregular formation of new bone. This and the absence of cupping at first at the growing ends of the bones give the *x*-ray picture a different appearance from that of rickets.

The Skull. Osteoporosis is particularly well marked in the skull. Calcification is so disorganized in this region that growth does not keep pace with that of the brain and the enlarged anterior fontanelle bulges. At first the sutures are widely separated, but later in the absence of normal growth at the margins, premature fusion of some of the sutures takes place, presumably due to amorphous calcification. This results in marked asymmetry of the skull with disproportionate growth, usually of the posterior part of the vertex, and a beaten silver appearance of the rest of the cranium. The anterior fontanelle finally closes later in a heaped-up prominence. It is interesting to note that craniostenosis has been reported in a case of vitamin D-resistant rickets (Coleman and Foote, 1954), possibly giving further support to the view that cessation of normal growth at the suture lines is the decisive factor.

Biochemical Changes. Deficient production of alkaline phosphatase, which is reflected by the low level in the blood, is not limited to the skeleton but is present in all tissues in which it is normally found

(Rathbun, 1948; Sobel *et al*, 1953). No excessive loss has been discovered in the urine (Sobel *et al.*, 1953), nor has any increased excretion in the faeces or bile been established.

A raised serum calcium level was present in two of our cases (C.A. and M.M.) and in three of the four cases quoted in the literature in whom it was estimated. A possible explanation of the hypercalcaemia is that calcium is piling up in the blood because of the reduced ability of the skeleton to form normal bone salts.

There is little doubt that renal insufficiency, and the raised blood urea which resulted, were due to the hypercalcaemia, and Rathbun (1948) did in fact find plugging of the collecting tubules, with casts and a surrounding low-grade inflammatory reaction. It is also known that hypercalcaemia from any cause can result in renal damage.

Treatment and Prognosis. Various forms of therapy have been attempted. The only one which seems to be of any avail is vitamin D in high dosage. This seems to encourage calcification. Nevertheless the blood phosphatase level continues to remain low indefinitely, despite the fact that vitamin D_2 has been found to activate alkaline phosphatase (Zetterström and Ljunggren, 1951). This again may well be the result of a primary osteoblastic deficiency. Although bone growth improves, radiological abnormalities persist in some cases, and defective bone formation is well illustrated in cases where osteotomies have had to be performed later to correct orthopaedic deformities (Schneider and Corcoran, 1950). Whenever high vitamin D therapy is employed, careful watch must be kept for toxic reactions, which can easily develop and may call for reduction in dosage. The ultimate fate of the skull has already been recorded and the danger of craniostenosis impairing vision has been emphasized.

The prognosis seems to depend mainly on three factors: the age at onset of symptoms, the degree of phosphatase deficiency and the severity of the associated renal lesion.

Summary

Three cases of a rare bone disorder are described in which calcification is defective. This has been proved to be associated with deficient production of alkaline phosphatase. It is suggested that the primary fault may be in osteoblast formation and that it would not be unreasonable to call this condition osteoblastic dysostosis. One of the main factors in the diagnosis is the discovery of hypophosphatasaemia, but hypercalcaemia is also present and may result in renal damage and nitrogen retention. This can prove fatal, but in less severe cases recovery can be expected and calcification of the affected bones ultimately takes place.

We are indebted to our colleagues both within and outside the hospital, already mentioned in the text, for their help and interest in the biochemical and radiological problems involved in these cases. Dr. Wilfrid Sheldon was one of the many physicians who examined the first case and it was he who directed our attention to this syndrome in the American literature. Dr. G. H. Bourne has been most generous in placing at our disposal the text of a book on the general subject of bone physiology and biochemistry, which has yet to appear in print.

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EPIDERMOLYSIS BULLOSA IN THE NEWBORN

BY

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Epidermolysis bullosa is an intractable skin condition characterized by the development of vesicles and bullae spontaneously or as a result of minimal trauma. It is usually hereditary and appears to be due to a congenital defect of skin structure.

It has been divided into a simple or non-scarring type inherited as a Mendelian dominant trait and a dystrophic or scarring variety of greater severity, in which the mode of inheritance is variable. Both forms may occur in infancy, and in addition Herlitz (1935) has described a further type which is invariably fatal and very rare.

Since relatively little has been published on this disease in the neonatal period in this journal, six cases are being presented which have been seen recently at hospitals in Edinburgh.

Cases 1, 2 and 3 are examples of the rare Herlitz type, and Cases 4, 5 and 6 of the more common dystrophic variety.

Case Reports

Case 1. T. McC., a boy, the third child of unrelated parents, was born spontaneously at full term in the Elsie Inglis Memorial Maternity Hospital, Edinburgh, after a normal pregnancy on October 3, 1952.

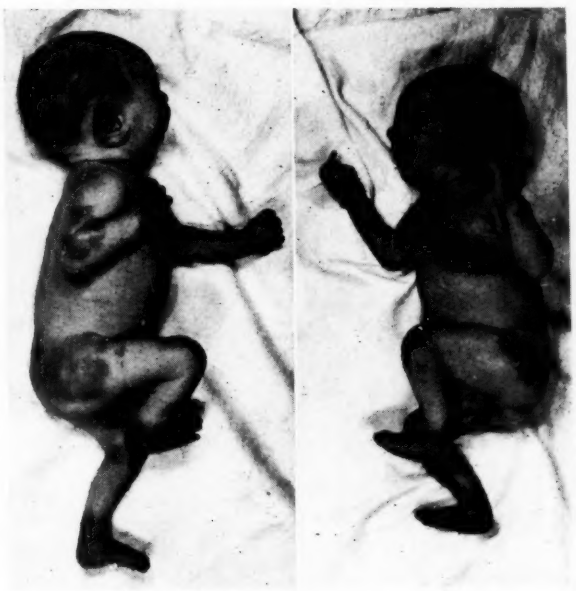
At birth, there were raw, red areas over the wrists, hands and feet, and along the extensor surfaces of the legs. The nails were long and horny. Within 24 hours further bullae containing sterile, straw-coloured fluid appeared over the sacral region. Nikolsky's sign was absent. The Wassermann reaction was negative in parents and child.

Subsequent progress was marked by the formation of widespread bullae over many parts of the body, including the buccal mucous membrane.

The infant's temperature on the fourth day rose to 104° F., and remained high subsequently despite therapy which included penicillin, streptomycin, chlortetracycline and oxytetracycline. *Staphylococcus aureus* was cultured from some of the later lesions. By the fourteenth day hoarseness of his cry and dysphagia were attributed to bullae in the larynx and pharynx.

The bullae healed without scarring in approximately seven days but fresh lesions appeared and the child's condition became poorer. However, the original raw areas that were present at birth had not healed when the child died. There was no leucocytosis and the blood chemistry was normal except for hypoproteinaemia. Urine analysis was negative, including examination for porphyrins.

Local measures, such as vaseline gauze dressings, kept the skin lesions reasonably clean but the infant continued to deteriorate (Fig. 1) and he died on January 10, aged 10 weeks.



1a 1b

FIG. 1.—Photographs showing skin lesions in various stages about two months before death. (Case 1.)

At necropsy there was widespread extensive epidermal ulceration, particularly severe over the thorax and abdomen. Bullae were still evident and varied in size from minute pin-head structures to large confluent vesicles. No involvement of the pharynx or alimentary tract was found. Post-mortem examination failed to reveal any specific pathological changes affecting the

internal organs and this was confirmed microscopically. Death could not be ascribed to any particular process and so the assumption remained that bacteriological or biochemical factors were ultimately responsible.

Sections of skin were taken from many diverse sites. These sections showed bullae in numerous stages of development (Fig. 2), the larger packed with polymorph leucocytes and obviously infected. The bullae appeared to begin in the stratum Malpighii just external to the basal cell layer, and consequently this layer together with the rete pegs remained intact—a feature that would account for the absence of scarring. The vesicles in enlarging had extended laterally, splitting the stratum Malpighii and finally coalescing as the thin intervening cellular partitions were ruptured. No inclusion bodies could be demonstrated.

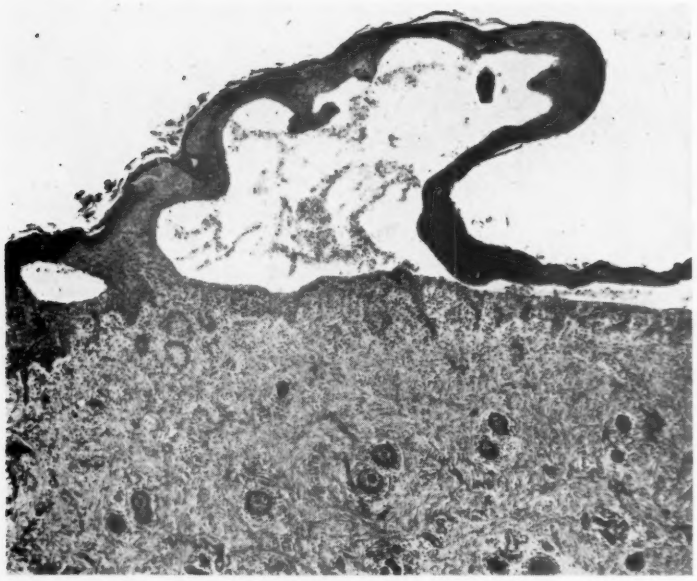


FIG. 2.—Skin section of Case 1 × 35, showing early bullous formation and separation of dermis.

In the dermis there was no specific pathological change, sections showing an apparently normal elastic element. Sweat glands were normal and serial sections failed to reveal any direct connexion between these glands and the epidermal bullae.

The stain for elastic tissue was Weigert-Van-Gieson's.

Case 2. D.M., a boy, was the first child of a consanguineous marriage (the parents being full cousins) born spontaneously at full term in the Simpson Memorial Maternity Pavilion, Edinburgh, after a healthy pregnancy on November 7, 1947. On the fifth day vesicular and bullous eruptions occurred in the napkin area and on the extremities, the lesions rapidly coalescing. The blisters ruptured and released seropurulent exudate, which on culture produced a growth of *Staphylococcus aureus*. Respiration was embarrassed by a blood-stained purulent nasal discharge. The infant was transferred to the Royal Hospital for Sick Children, Edinburgh, on December 7. There were extensive raw areas over the trunk, especially the buttocks, and on the limbs from which a seropurulent fluid exuded (Fig. 3). Fresh bullae continued to appear on these areas and also on the lips.

FIG. 3.—Photograph showing extensive skin involvement in Case 2.

The Wassermann reaction of both parents was negative.

The organisms cultured from the lesions being penicillin resistant, he was given systemic and local streptomycin therapy. He was nursed exposed. His temperature became remittent after tending to settle initially, and continued until his death on December 25 at the age of 7 weeks. Throughout his illness there was a moderate leucocytosis. Other therapy was tried both systemically and locally to combat infection and to provide protection but the child's condition progressively deteriorated.

At necropsy, in addition to the extensive skin lesions, bilateral bronchopneumonia was found secondary to aspiration of the gastric contents. No special studies of the skin histology were made.

Case 3. G.M., a boy, was the fourth child of the same parents. Again pregnancy and delivery had been normal but this time the birth was at home on February 21, 1953.

Blistering of a thumb and the umbilical area was said

to be present from birth and further bullae developed rapidly despite the local application of gentian violet. The infant developed 'snuffles' and on admission to the Royal Hospital for Sick Children, Edinburgh, on March 27, many intact as well as broken and secondarily infected bullae were present over the trunk and limbs, on the lips and in the mouth. There was a mucopurulent nasal discharge. Syphilis was excluded and antibiotic therapy was instituted. The child was nursed exposed, but despite this and other local measures deterioration was progressive and further bullae developed (Fig. 4).

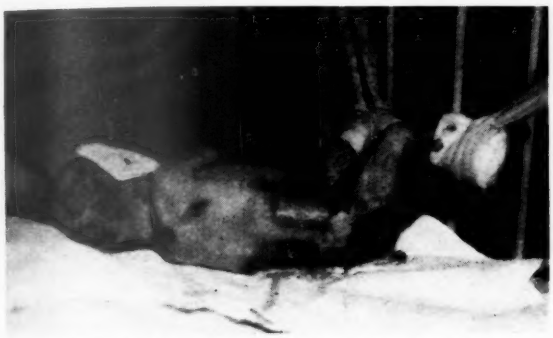


FIG. 4.—Photograph of Case 3 just before his death.

He ran a remittent fever but there was no leucocytosis. Terminally, the nails of the hands and feet became detached or deformed and he died in his tenth week on April 28.

At necropsy there were large raw areas on the skin over the occiput, elbows, abdomen, buttocks, sacrum, legs and heels. Some of the ulcerated areas were covered with dry crusts, others had a slightly moist, bright red surface. No bullae remained. The skin, even where intact, was easily torn.

There was a blood-stained serofibrinous effusion in the right pleural sac. Both lungs contained large areas of consolidation: in the heart a roughened area on the posterior cusp of the tricuspid valve may have been the site of a thrombus that had become detached. Antemortem thrombus was found in the left ventricle attached to the chordae tendinae and anterior cusp of the mitral valve. There was a recent infarct in the spleen.

Bacteriological examinations revealed *Streptococcus haemolyticus* in the blood, and the same organism along with *Staphylococcus aureus* in the lungs and pleural exudate.

Microscopical sections of the skin from a number of parts showed that where the surface was denuded of epithelium the cutis was densely infiltrated by polymorph leucocytes. In parts with intact epithelium there was no inflammation and the skin glands, hair follicles and elastic tissue appeared normal.

The consolidated areas in both lungs proved to be septic infarcts. Some of those in the right lung had proceeded to abscess formation. Arteries related to these areas contained thrombi, which may have been of embolic origin from the tricuspid valve. Both kidneys had calcified casts in the collecting tubules, and showed the typical picture of medullary nephrocalcinosis at an early stage.

The findings in this case were so similar to those of his elder brother (Case 2) that the diagnosis of skin sepsis made in the latter was revised to that of epidermolysis bullosa hereditaria letalis. The family details are depicted in Fig. A.

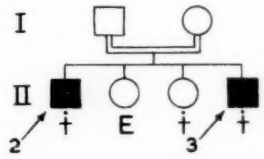


FIG. A.

Case 4. M.C., a girl, was the first child of healthy, unrelated parents born at term in an Edinburgh nursing home after a healthy pregnancy on July 13, 1948. Small white spots on the tongue and an inflamed area on the roof of the mouth were noted shortly after birth. Subsequently blisters appeared on the hands, feet, and buttocks. She was admitted to the Royal Hospital for Sick Children, Edinburgh, on July 19 aged 6 days.

On examination, she was well nourished and adequately hydrated. There were bullous lesions on the fingers, toes, trunk, and also on the buccal musosa. The contents of the lesions were clear or occasionally haemorrhagic and no growth was obtained on culture. There was no leucocytosis. The maternal Wassermann test was negative.

The child fed well but did not gain weight. She was afebrile but fresh lesions appeared on the hands, feet and trunk. Treatment, none of which was effective, consisted of several local applications including gentian violet, and sulphonamide creams and also systemic penicillin and sulphonamide. Finally after a diagnosis of epidermolysis bullosa had been suggested the parents requested her discharge on August 30 and she died a few days after her return home. There was no necropsy.

Case 5. D.C., a boy, was the third child of the parents of Case 4 and was born spontaneously at full term in an East Lothian hospital. Blisters were noted at birth, and when he was seen as an out-patient in Edinburgh two days later bullae were present on the right thumb, scrotum, thighs and upper alveolar margins. A diagnosis of pemphigus neonatorum was made and penicillin therapy instituted. A culture of the bullous fluid grew *Staphylococcus albus* and a non-haemolytic streptococcus.

The child's subsequent progress was stormy, for slight trauma such as a hard rubber teat or firm handling produced bullae. Lesions occurred over the buttocks, in the axillae, and on the extremities. The bullae contained serous or sometimes haemorrhagic fluid.

When he was seen in June, 1953, at the age of 2 years 4 months, the child was well developed mentally and physically. He had thin atrophic scars on the hands, feet, over the knees, and near the axillae. Small epidermal cysts were to be seen in the scars. He had an unruptured haemorrhagic bulla at the base of the left thumb. The left thumb-nail was thickened. He had no defects of hair or teeth.

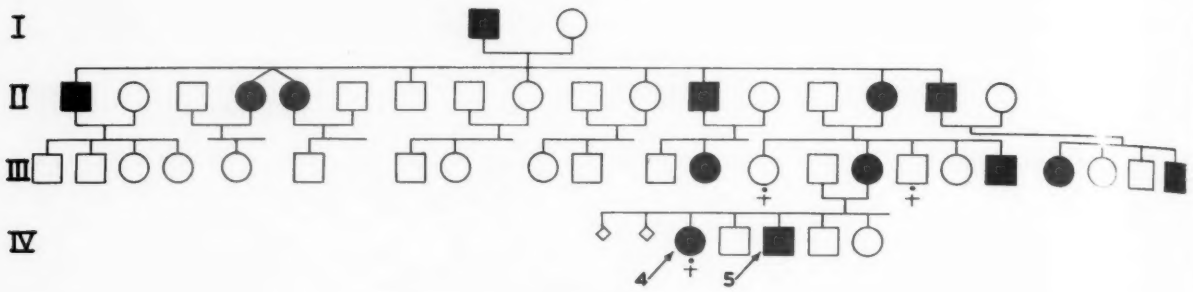


FIG. B.

There were two other unaffected children in the family and the elder child's birth had been preceded by two miscarriages.

The condition was inherited from the mother and her family, the affected members having deformed nails and scarring to a greater or lesser extent.

The family history is depicted in Fig. B.

Case 6. D.F., a boy, was the second child of healthy, unrelated parents and was born spontaneously on July 17, 1952, in the Simpson Memorial Maternity Pavilion, Edinburgh, after a healthy, full-time pregnancy.

The maternal Wassermann test was negative.

A nurse noticed a blister on the right heel one week after delivery and on his return home further blisters developed on the feet and hands and the right thumb-nail came off. Since then he has had bullae over the trunk as well as the limbs and also in the mouth, the contents at times being serosanguineous.

When examined as an out-patient in June, 1953, at the age of 1 year, he was an active, well developed child. He had bullae in various stages of development and healing on the hands and feet (Fig. 5). Previous lesions had left thin atrophic scars containing minute epidermal cysts. The right thumb-nail and right fifth toe-nail were deformed and thickened.

His father and his family gave a history of a similar abnormal response to trauma. The child's elder sister was perfectly normal.

The family tree is depicted in Fig. C.

FIG. 5.—Photograph of Case 6 showing fresh bulla on child's knee and scars of old lesions. The limb is held by his father whose deformed thumb nail can be seen.

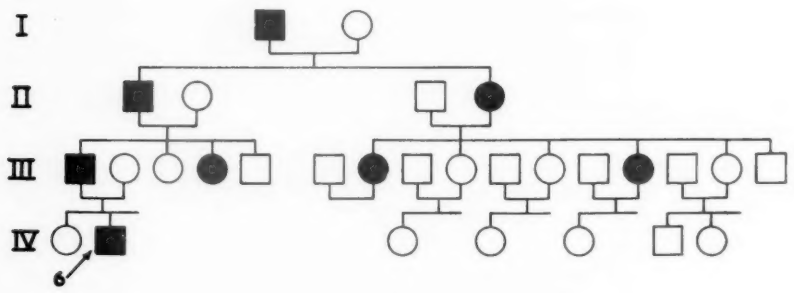


FIG. C.

Discussion

Bullous eruptions occurring in the neonatal period may be due to any one of a number of unrelated conditions. The prognosis varies with each disease as does the treatment, and early diagnosis is therefore important.

The table gives the main criteria for diagnosing bullous eruptions.

TABLE

BULLIOUS ERUPTIONS IN THE NEWBORN

Disease or Condition	Aetiology	Character of Lesions	Distribution	Mucosal Involvement	Other Ectodermal Defects	Scarring	Response to Drugs	Course
Epidermolysis bullosa	Congenital skin defect	Clear blisters; sometimes haemorrhagic non-inflammatory base	Sites of trauma or friction	Yes	Yes	Yes or no	Nil	Chronic or fatal
Bullous impetigo	Staphylococcal	Blisters, clear, opaque, purulent	General, particularly flexures	Possible	No	Yes	Antibacterial drugs	Short
Congenital spyhilis	*Trep. pallida*	Bullae and maculopapules	Palms, soles, trunk and limbs	Yes	Yes	No (other than rhagades)	Antiluetic	Short
Dermatitis herpetiformis	?	Vesicles and bullae in crops, also urticarial lesions	In infants face and limbs chiefly involved	Sometimes	No	Minimal in long-standing cases	Arsenic and sulphones	One-third curable. Chronic or recurrent
Burns	Hot bottles	Erythema, bullae, desquamation	Anywhere	No	No	Yes if deep	—	Depends on type, depth, and therapy
Congenital porphyria	Hereditary metabolic disorder	Red urine, photo-sensitivity of skin, erythema, bullae	Areas exposed to sunlight	No	Pigmented teeth	Pigmented scars	Nil	Chronic
Erythema multiforme bullosa	Allergy ?	Dusky red circinate plaques, papules, bullae	Trunk, limbs, face	Yes	No	No	Topical only	Short or recurrent
Dermatitis medicamentosa	Drug allergy: iodides, bromides, phenolphthalein	May be vesicular	No particular site	No	No	No	Topical only	Short
Papular urticaria	Allergy	Papules, bullae,	Trunk only or limbs	No	No	No	? Antihistamines	Short or recurrent
Chickenpox	Virus	vesicles, pustules	Trunk, face, limbs	Yes	No	Yes	Nil	Short
Smallpox	Virus	Vesicles, pustules	Limbs, trunk, face	Yes	No	Yes	Nil	Short
Kaposi's varicelliform eruption	Virus	Vesicles, pustules	Exposed parts	No	Pre-existing skin disease of infantile eczema or Besnier's prurigo	No	Antibacterial drugs for secondary infections	May be fatal
Herpes zoster	Virus	Vesicles	Classical girdle	No	No	Yes	Nil	Short
Bullous erysipelas	Group A haemolytic streptococci	Raised tender erythema, bullae	Peri-umbilical, limbs, face, trunk	Rarely	Nil	Nil	Antibacterial drugs	Short with therapy
Benign familial pemphigus (Hailey's disease)	Familial	Vesicles and bullae	Anywhere	No	No	Nil	Possibly sulpha drugs and antibiotics	Benign chronic
Contact dermatitis	Allergy	Often vesicles and bullae	Anywhere	No	No	No	Removal of sensitizing agent	Short
Phytophotodermatitis	Occurs when skin sensitized by contact with certain plants is exposed to sunlight	Vesicles and bullae	Areas exposed to sunlight	No	No	No	Nil	Short
Acrodermatitis enteropathica	May be vitamin deficiency or bowel infection	Crops scaling, vesiculobullous	Near orifices, around eyes, elbows, knees, hands, feet	Yes	Hair scanty	No	? Diodoquin	May be fatal

Pemphigus vulgaris is never seen in infancy or early childhood

In epidermolysis bullosa, the bullae occur at the points of trauma or of pressure. The usual sites of lesions in the baby are the toes, heels, buttocks, scapular regions, axillae, elbows, fingers, ears and occiput. In older children, the hands and fingers, elbows, knees and toes are more often affected. The contents of the bullae may be serous or haemorrhagic and are sterile on culture. The fingers and toe-nails are frequently thickened and deformed or may be absent. The diagnosis is based on the finding of these features. Nikolsky's sign—the ready detachment of the horny layer of the skin by trauma—mentioned by some as a valuable diagnostic aid, may not be present, but in any case it is found in other bullous skin diseases.

There are several theories on the aetiology of the disease but none has been accepted universally. These include endocrine upset, increased irritability of the cutaneous vascular system, congenital neurovascular anomaly and sympathecotonia, but it is now widely accepted that there is some inherited disturbance of the skin structure. Several workers have suggested that it is due to an absence or deficiency of elastic fibres in the papillary and subpapillary layers of the skin. Kanoky and Sutton (1910) stated that this deficiency was general and that it was not confined to the affected areas. Excess urinary porphyrins were found in some cases (Turner and Obermayer, 1938) but it is probable that these were really examples of congenital porphyria. A German article (Langhof, 1952) postulated an upset in hyaluronidase metabolism, due to a deficiency in a serum heparin-like substance. The latest paper (McDaniel, 1954), recording a severe dystrophic variety with recessive inheritance, described complete absence of elastic tissue in the upper half of the dermis.

Males are affected more frequently than females and the disorder is found in all races. The onset may be at birth or shortly after but in the less severe types the lesions may not appear for months or even years.

The pathology of the rapidly fatal form has been described in several papers. Herlitz (1935) mentioned that the skin was thinner than usual with degenerated elastic fibres and rudimentary hair follicles and sweat glands. Lamb and Halpert (1947) stated that the corium was loose, fibrillar and relatively acellular, but they mentioned that normal collagenous bundles, hair follicles, sebaceous and sweat glands were present. Normal skin glands were mentioned by Schäffer (1951) but he found a thin epidermal layer, and, while the amount of elastic tissue was reduced, the elastic filaments were not entirely atrophied. Matheson and Rosner (1949) considered that there was deficient elastic tissue in the superficial layers of the skin. In the two fatal cases in our series which were studied in detail, no abnormality of the histological structure of the skin was found. In Case 3, secondary infection obscured any clinical features of nephrocalcinosis that might have been present and also the picture at necropsy.

The two main types of the condition have been mentioned previously. The simple variety produces lesions which heal in from two to 10 days, leaving no scar. The mucous membrane is involved in very few patients. Most of those with this type of epidermolysis improve at puberty.

The dystrophic variety has been subdivided into three (Cockayne, 1933). The first type, which is inherited as a dominant trait, does not interfere with growth or development. The lesions may be severe over the hands or toes and over other points liable to trauma or pressure. Finger- and toe-nails may be lost and on re-growth are frequently thickened or deformed. The scars, which result on healing, are thin and atrophic and may contain small epidermal cysts. Puberty may produce improvement or else the abnormal traumatic response may persist throughout life. Cases 4 to 6 were of this group and the fact that the trait is inherited as a dominant is shown by the family trees (Fig. B and C). These reveal that the condition is transmitted by affected members of either sex. Another feature is that the sex ratio is equal in both these families. Case 4 shows that the prognosis must be guarded although secondary infection may have been responsible for this fatality. Her brother (Case 5) who survives, presented a difficult nursing problem. He had to be wrapped in cotton wool to prevent the formation of extensive bullae. Handling had to be reduced to a minimum and required great care. Even feeding was a problem as a rubber teat, unless softened by repeated boiling, blistered the child's mouth and gums.

The second type seems to be inherited as a recessive and in many cases the children are undersized and below normal intelligence. The teeth may be more liable to caries and the mucous membranes of the alimentary and respiratory tracts are frequently affected. Few survive to maturity.

Cockayne's third variety contains miscellaneous conditions showing features of both epidermolysis and congenital ectodermal dysplasia.

The form described by Herlitz (1935), which he called epidermolysis bullosa hereditaria letalis, shows the following features: (1) It begins at birth or soon after. (2) Death usually occurs before the third month of life. (3) There is marked deformity of the finger- and toe-nails or some of these nails

may be missing. (4) The bullae of the skin or mucous membranes may be haemorrhagic. (5) Nikolsky's sign may be present but the production of blisters by experimental trauma is unsuccessful. (6) Healing takes place without scarring. (7) The inheritance is recessive. In some cases no history of the condition exists previously, in others the parents were first cousins and more than one case may occur among siblings. (8) There are congenital skin defects such as a thin corium, a reduction in the number of sweat glands and hair follicles. The elastic tissue is diminished. (9) Skeletal atrophy may occur near areas of skin showing localized congenital defects.

Since Herlitz's paper other examples of this fatal form have been described (Davidson, 1940; Brandberg, 1941; Schroder and Wells, 1945; Black, Wilhelm, Gilbert and White, 1945; Lamb and Halpert, 1947; Matheson and Rosner, 1949; Schäffer, 1951; Kagen, Williams, Giffen and Wiley, 1952; and Leland and Hirschl, 1954). The paper by Leland and Hirschl stated that before their own paper, which added two further examples, 32 patients with epidermolysis bullosa hereditaria letalis had been reported in the world literature but clinical features as well as the pathology have differed from the details given by Herlitz. For instance, one of the patients recorded by Kagen *et al.* (1952) lived for 16 months.

In the present series Cases 1 to 3 were considered to represent the condition of epidermolysis bullosa hereditaria letalis. Most of the features stipulated by Herlitz were present although bone atrophy did not occur and it was difficult to decide whether lesions healed without scarring in Cases 2 and 3 because of their early deaths.

The parents of the brothers (Cases 2 and 3) were first cousins, a feature in two of the three families studied by Herlitz. Case 1 was born of unrelated parents and there was no known history of bullous conditions in previous generations.

One surviving sister of Cases 2 and 3 is subject to grand mal type epilepsy. Another child died of multiple congenital anomalies a few hours after birth.

The prognosis in epidermolysis bullosa must depend on the type. In the simple varieties it is excellent, and the condition should improve about puberty in most cases. In the dystrophic forms it can be more serious, and Cockayne mentioned a recessively inherited fatal variety which may have included cases similar to those described by Herlitz. In epidermolysis bullosa hereditaria letalis, death occurs almost invariably within three months of birth.

The common dystrophic type (Cases 4 to 6) may have serious consequences, as in the baby in Case 4 who died of blistering with sepsis in early infancy. Secondary infection and difficulties in management are the two dangers. Cases 5 and 6, while both are liable to severe blistering, are normal, lively youngsters who do not allow their skin disability to interfere with their activity.

No effective treatment has been found although in a recent article Langhof (1952) claimed to be able to prevent blistering using an ointment containing heparin. He claimed protein shock therapy was also effective. He postulated a disturbance in hyaluronidase metabolism and a deficiency of heparin or a heparin-like substance in the tissue fluid. He stated that hyaluronidase, if administered, increased the number and size of bullae in a case of epidermolysis. Supplies of the heparin ointment 'thrombophob' were obtained from Germany and administered to Cases 5 and 6. It was rubbed into the hands and knees three times daily but in neither case was blistering prevented although one mother thought that the blisters were not so big. This mother, however, felt that equally good, if not better, results were obtained using an antihistamine locally and parenterally.

As one cannot cure or control the condition, the aims of therapy must be (1) to handle carefully so as to prevent bullae forming; (2) to limit the spread of established bullae; (3) to prevent secondary infection and hasten healing.

In the baby, the first aim can be served by a thick wrapping of cotton wool, and infrequent and careful handling. In the older child, however, it is almost impossible to prevent trauma in an active and otherwise healthy child.

The second aim is easily executed. Blisters should be snipped as soon as they appear and the contents expressed.

The third point does not seem such a problem in the older child as in infancy; cleansing the skin with 1% cetrimide, and the application of a sterile, non-boric-containing talc preparation is recommended in babies, but in older children a drying paste should be applied. The mother of one of our cases, a doctor's wife, has, after many trials, found Lassar's paste to be the most effective. Infection, particularly in babies, should be countered by adequate systemic antibiotic therapy as well as by local applications.

As might be expected in a disease of unknown aetiology, corticotrophin (A.C.T.H.) and cortisone have been tried but without benefit (Lever, 1951; Jensen, 1951; Cannon, Hopkins, Andrews, Colfer,

Gross, Nelson and Howell, 1951; Leland and Hirschl, 1954).

Summary

Six cases are recorded of epidermolysis bullosa in infants. Three of them were the rare recessive form known as Herlitz disease; the other three were the dominant dystrophic variety.

The aetiology, pathology, clinical features and methods of treatment of the disease are discussed, and a table is given of the points for differential diagnosis of bullous eruptions in the newborn.

All cases of the Herlitz type and one of the others died. No abnormality of skin structure was found in the two cases of Herlitz disease which were examined after death.

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CHRONIC CONSTRICTIVE PERICARDITIS COMBINED WITH HYPOPROTEINAEMIA

BY

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Constrictive pericarditis usually affects males in the third and fourth decades of life (Paul, Castleman and White, 1948; Chambliss, Jaruszewski, Brofman, Martin and Feil, 1951), but is rare under the age of 10. Rothstein (1934) collected 34 cases from the literature in children up to 15 years old, who had been operated on, but only 12 were younger than 10. More reports have appeared since, but the children are now usually included in large series of patients who have undergone an operation. It is often impossible to select the children from those series and thus to establish any special features that might occur in childhood, for instance hypoproteinaemia, as has been suggested by McKusick (1952). The rarity of the disease in children, together with the difficulties we originally had in making the diagnosis, have prompted the following case report.

Case Report

On March 3, 1954, a 7-year-old boy was referred to the Children's Clinic for investigation of hypoproteinaemic oedema and ascites. He was the eighth of 11 children. The family history contributed nothing but the boy had been treated badly during the first six months of life and a state of malnutrition had developed. He was then brought up by step-parents on a farm and he had not been ill since.

An inguinal hernia was operated upon in February, 1953. Much fluid had appeared from the abdominal cavity. The boy had made an uneventful recovery. During the summer he had measles and chickenpox, and afterwards oedema of the face and feet was noted. His appetite decreased and periodically he had loose stools. During clinical observation elsewhere (August, 1953) an enlarged liver and ascites were found. The blood protein levels were low (Table 1), the cholesterol content of the blood was normal (Table 2) as were the temperature and pulse rate. No protein could be demonstrated in the urine. A series of liver function tests did not show any abnormalities. No tubercle bacilli could be cultured from the ascites. A needle biopsy of the liver did not show histological abnormalities. The tuberculin test of the skin was negative. The boy now had a ravenous appetite. His condition improved although the blood protein levels did not change much, and even showed a

TABLE 1

LEVEL OF BLOOD PROTEIN (METHOD OF HOWE) ON VARIOUS DATES

Date	9/8 1953	9/17	9/29	10/19	1/28 1954	2/23	3/3	4/14	7/8
Albumin ..	3·54	3·3	3·17	3·08	2·58	2·63	2·53	2·45	4·64
Globulin ..	0·96	1·9	1·93	1·62	1·42	1·72	1·37	0·92	1·4
Total ..	4·5	5·2	5·1	4·7	4·0	4·35	3·9	3·37	6·04

Electrophoretic fractionation according to the Tiselius method: albumin 19·32, α-globulin 5·91, β-globulin 6·54, γ-globulin 3·22 g/l. Total serum proteins = 34 g. per l.

TABLE 2

BIOCHEMICAL DATA AND LIVER FUNCTION TESTS ON VARIOUS DATES

	Sept., 1953	Feb., 1954	April, 1954
E.S.R. (mm. in 1 hour Westergren)	4	2	3 to 6
Alkaline phosphatase level (Bodansky units)	10·1	6·7	9·0
Cholesterol (mg./100 ml.serum)	170	185	141
Esters (%)			74
van den Bergh test: direct ..	Negative	Negative	
indirect	Trace	Negative	
Urea (mg./l. blood)	333	250	386
Thymol turbidity (units) ..			3
Bromsulphalein test (40mg. intravenously)			Neg. after 30′
(value after 3′ = 100%) ..			45% after 6′
			Neg. after 30′
Urobilinuria	Negative	Trace	
Galactose tolerance (excretion after ingestion of 24 g. by mouth)	0·04 g.		0·16 g.
Basal metabolic rate			+1%
Neutral fat in faeces } % wet			0·3
Fatty acids in faeces } weight			1·3

Blood sugar levels (mg./100 ml.) fasting and at various times after the ingestion by mouth of glucose and fructose

	0	After 30′	60′	90′	150′
30·0 g. glucose ..	119	179	189	165	93
36·5 g. fructose ..	105	126	133	121	122

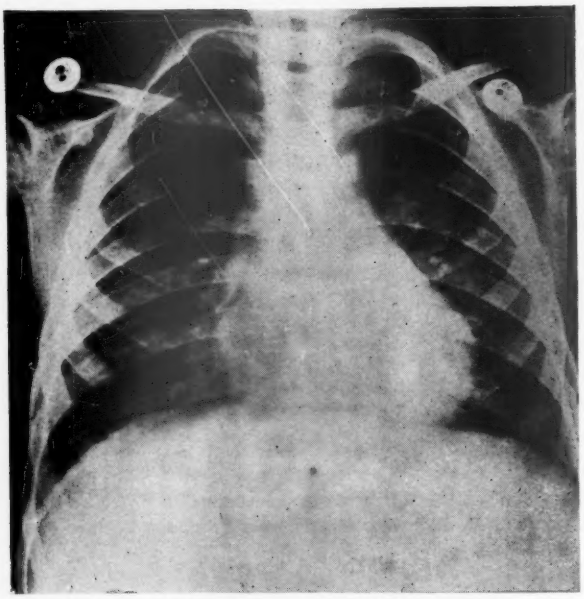


FIG. 1.—Radiograph of the heart before operation.

tendency to decrease (Table 1). He was treated with a diet poor in salt, but rich in proteins plus methionine and vitamin B complex and liver injections. Shortly after a purulent otitis the ascites again increased considerably and he was readmitted at the end of January, 1954. Biochemical results were as before, and he was transferred to the Children's Clinic for further investigation.

We found a short, stubby boy (somatic development about 5 years old) with a considerably enlarged chest circumference similar to that of a child of 11 years. His weight was 21 kg. He was in no apparent distress but on exertion easily became dyspnoeic. No cyanosis was present, the respiration rate being about 20 per minute. His face was puffy and slight oedema was present around the eyelids. The heart sounds were normal. The liver edge was felt 5 cm. below the costal margin and the presence of free fluid in the abdominal cavity could easily be demonstrated. Compared with slight oedema in the legs the amount of ascites was considerable. Blood pressure measured 95/60 mm. of mercury, and engorgement of the neck veins with pulsations of a level about 4 cm. above the angle of the sternum indicated an increased venous pressure. No protein or other abnormality could be demonstrated in the urine. Urobilinuria was sometimes increased.

Chronic constrictive pericarditis was suspected. The heart seemed to be somewhat enlarged to the left (Fig. 1) but pulsations were thought to be normal during fluoroscopy and no deposits of calcium could be seen. The radiokymograph demonstrated fair pulsations of the left border of the heart (Fig. 2). Although the right border did not pulsate this was not accepted as evidence of constrictive pericarditis, because the auricles generally do not show evident pulsations on a kymograph. An electrocardiogram demonstrated right axis deviation in the standard limb leads and severe right axis strain in the V leads. The height of the excursions was thought to be normal, although in several leads the P and the T waves could barely be distinguished (Fig. 3).

The diuresis measured between 200 and 400 ml. per day, while the fluid intake was free (about 700 to 1,000 ml. per day). The specific gravity of the urine was 1,020 or more. The daily output of chlorides was less than 5 mEq., but the salt in the diet was restricted.

During the first fortnight of observation the level of the pulsations in the veins of the neck decreased gradually until it corresponded with the level of the angle of Louis measured by the method of Borst and Molhuysen (1952). The body weight remained fairly constant and no change occurred in the size of the liver nor in the amount of the ascites. In the meantime a series of liver function tests gave normal results, including two bromsulphthalein tests (Table 2). Also the tuberculin test with 1 mg. of old tuberculin was negative, as were serological tests for syphilis.

So far we had not obtained a satisfactory explanation for the syndrome of oedema, enlargement of the liver, ascites, increased venous pressure and hypoproteinaemia. Malnutrition, the nephrotic syndrome or cirrhosis of the liver could be ruled out. In spite of the changes in the electrocardiogram and the increased venous pressure heart failure seemed unlikely, because two bromsulphalein tests and the circulation time were normal. No evidence of chronic constrictive pericarditis had been found on the *x*-ray pictures.

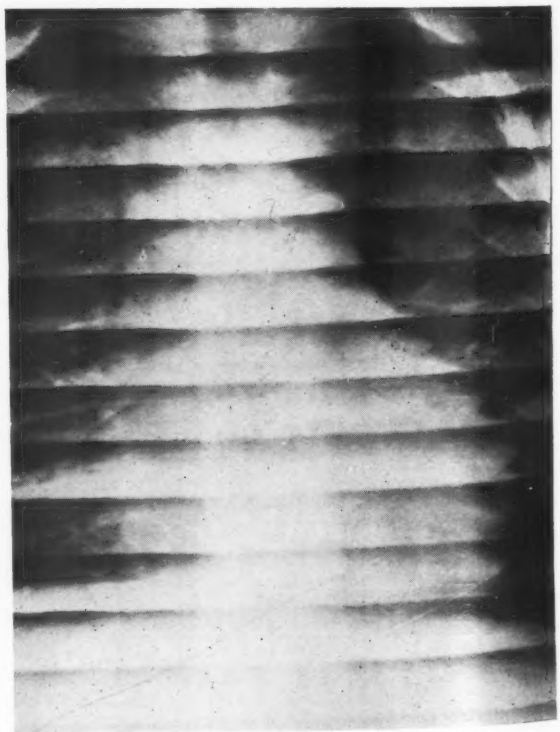
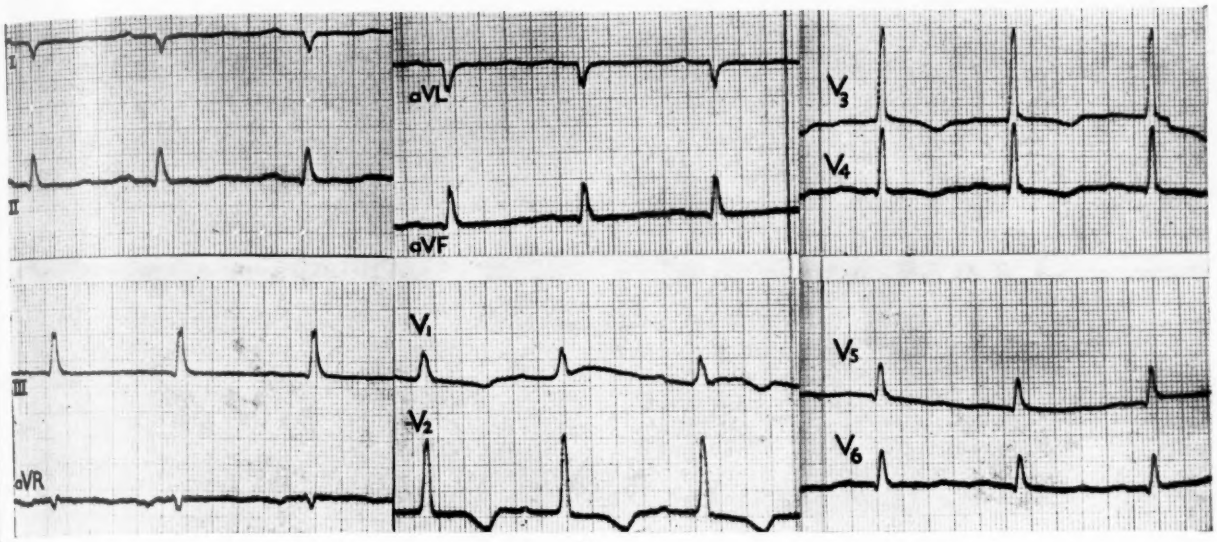


FIG. 2.—Radiokymograph before operation.



a b c

FIG. 3a-c.—Electrocardiogram showing right ventricular strain.

We first decided to investigate the effect of digitalis on the diuresis and on the increased venous pressure. The diuresis increased to 550 and 700 ml. during the first two days of digitalization with the equivalent of 100 mg. digitalis per day. However, the backward failure of the right heart got worse. The venous pressure rose to more than 5 cm. above the sternal angle (Lewis, 1930; Borst, 1943; Borst and Molhuysen, 1952) orthopnoea and moist râles indicated acute congestion of the lungs. An inconstant triple rhythm was heard and a paradoxical filling of the pulse was noted. The temperature then suddenly rose to 39·6° C. but with the aid of penicillin and the withdrawal of digitalis the boy managed to weather this period of severe congestive heart failure with respiratory infection. The increased venous pressure dropped gradually. Ten days later the improvement was such that catheterization of the heart was possible to obtain further information about the circulatory relations in the heart (Dr. M. L. M. Houben).

The catheter could easily be brought into the branches of the pulmonary artery. No abnormalities were found in the vessels or in the septum of the heart. The pressure curves of the right chambers, however, showed certain peculiarities characteristic of constrictive pericarditis. These changes were indicated for the first time by Bloomfield, Lauson, Cournand, Breed and Richards (1946), and have been elaborated extensively by Hansen, Eskildsen and Götzsche (1951), Yu, Lovejoy, Joos, Nye and Mahoney (1953) and Tourniaire, Blum, Deyrieux, and Tartulier (1953). They have been aptly summarized by Yu *et al.* as follows:

> 'The auricular pressure curve shows a M-or-W-shaped pattern, with two upward and two downward deflections, both failing to reach the base line. The mean pressure in the auricle is moderately elevated. The right ventricular pressure curve shows a slightly elevated systolic pressure and a rapid diastolic dip followed by a high diastolic plateau and high diastolic end-pressure. The ratio of the diastolic end-pressure to systolic pressure is more than one-third. The diastolic plateau is the expression of the diastolic filling defect being the essential haemodynamic change in constrictive pericarditis. The plateau has disappeared in patients successfully operated.'

When failure of the right ventricle is present in conditions such as stenosis of the pulmonary artery, mitral stenosis or severe emphysema, diastolic end-pressure can be elevated also. Yu *et al.* investigated 132 patients, but always found the ratio between diastolic end-pressure and systolic pressure to be less than one-third in conditions other than constrictive pericarditis. In our case this ratio varied between one-half and two-thirds. The pressure curve during withdrawal

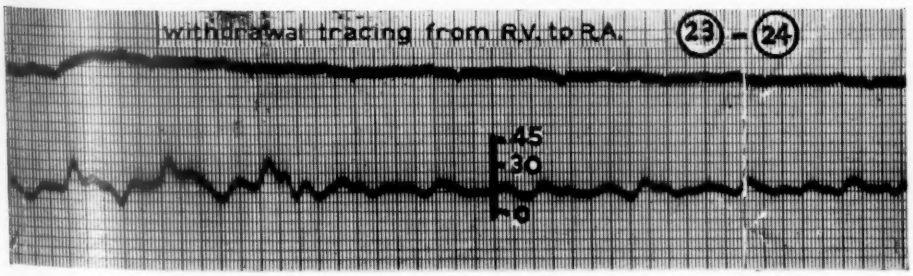


FIG. 4.—Electrocardiogram showing the pressure curve as the catheter was withdrawn.

of the catheter from the right ventricle is shown in Fig. 4. The pressures in the caval vein and in the right auricle were considerably elevated (maximum 20, minimum 10 mm. of mercury), while the diastolic pressure in the right ventricle was especially increased (20 to 24 mm.). The fluctuation of the pressure curve in the ventricle increased abnormally during deep respirations (f.i. 40/30 and 18/12 mm. respectively), a demonstration of paradoxical filling of the pulse. The oxygen saturation varied between 65 and 70% in the right heart chambers and in the pulmonary artery. In the 'capillaries' of the lung artery a saturation of 93% was found. The mean pressure there was rather high (about 20 mm.) and the fluctuations were large. This indicates serious involvement of the left ventricle (Sawyer, Burwell, Dexter, Eppinger, Goodale, Gorlin, Harken and Haynes, 1952), indicating that the surgeon should liberate the left side first (Isaacs, Carter, Noland and Haller, 1952).

In this case cardiac catheterization led us back to the right track again, but we might have made the correct diagnosis earlier had we taken to heart the advice of Barroy and van Heerswynghels (1946), who demonstrated layers of calcium in the pericardium by means of extra hard *x* rays. By this technique calcium could be demonstrated (Figs. 5 and 6) over the left ventricle in our patient also. The radiokymogram had been thought to show normal pulsations, but perhaps electrokymographic analysis (McKusick, 1952) would have prevented this assumption. Unfortunately no facilities to apply this method were available in this hospital.

In the next two weeks the condition of our patient improved further, the level of the pulsations in the neck veins dropping to below the sternal angle. The amount of ascites was plainly diminishing. However, the spontaneous improvement did not continue and the oedema and ascites were again progressing. The effect of a mercurial diuretic was only of very short duration. The only effective treatment was clearly resection of the pericardium. This was performed by Professor I. Boerema on June 14.

After a median incision the sternum was split and a few adhesions between the pericardium and the chest wall were removed. The heart was enveloped by a pergameneous pericardium, that also adhered to the epicardium. The adhesions were easily loosened. First the left ventricle was liberated, then the right ventricle and finally the mouths of the large veins also. Next the myocardium turned out to be covered by a thick new layer of fibrous epicardium. This was also removed for the most part. A small haemorrhage at the level of the auricles was stopped in a few moments. The whole myocardium had become bare, with the exception of a fibrinous cover in the region of the tip of the heart. The pulsations of the heart were visibly improved and the chest wall was closed. The first day after operation the boy was orthopnoeic and he was put into an oxygen tent. Soon his condition improved, the heart action became regular, and he lost the oedema. Also the ascites and the enlargement of the liver disappeared in a few weeks. The QRS waves increased somewhat in height. The volume of the heart increased also, as could be shown by radiographs and fluoroscopy (Fig. 7). Three weeks after the resection of the peri- and epi-cardium the blood proteins had become normal (Table 1). The patient was

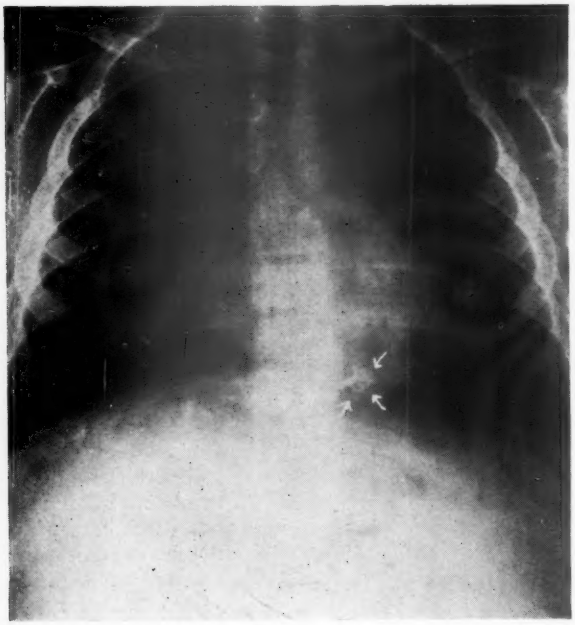


FIG. 5.

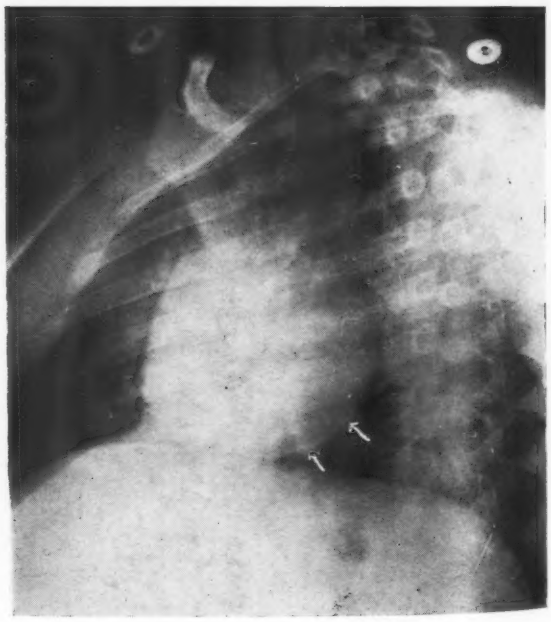


FIG. 6.

FIGS. 5 and 6.—Arrows point towards calcium deposits in epicardium.

discharged in a very much improved condition, the venous pressure being normal (level of the pulsations 3 cm. below the sternal angle).

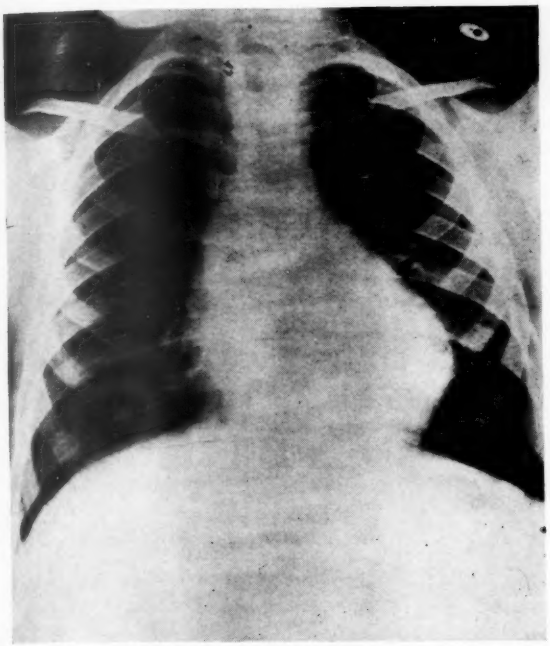


FIG. 7.—Radiograph of the heart after operation. Augmentation in volume (compare with Fig. 1).

Discussion

The syndrome of constrictive pericarditis is rare, especially in children, although dense, scar-like adhesions of the pericardium are found in 2 to 4% of all necropsies (Moschcowitz, 1953). Large surveys on diagnosis and treatment have been published during recent years by Holman and Willett (1949), Paul *et al.* (1948), White, Alexander, Churchill and Sweet (1948) and Chambliss *et al.* (1951). No special attention has been paid to differences in the syndrome at various ages, but McKusick (1952) mentions the possibility that the association of constrictive pericarditis with hypoproteinaemia might be a special feature in children. In the large series no separate reports are given about children but a few observations (McQuarrie, 1942; Stadler and Stinger, 1941) support this assumption. Moreover the first patient of Barroy and van Heerswynghels (1946) was reported to have a total level of blood proteins of 3·74% (albumin 1·675%); this girl was 7 years old. Another girl of 11 had a level of 6·55% of blood proteins. In McKusick's (1952) series of 20 patients six had a serum albumin level of 3·5 g. per 100 ml. or less. All these patients had had the disease from at least the early 'teens. With one exception they were more than 20 years old when they were investigated. These figures do not differ very much from those given by Chambliss *et al.* (1951), who found an average of 3·46 g. albumin per 100 ml. of serum in 39 patients, most of them adults. In 44 of their patients total blood proteins averaged 6·0%, the patients with oedema having an average of 0·5 g. blood proteins less than those without oedema. The degree of hypoalbuminaemia in young children is evidently lower than in adults, even when only the method of Howe is used for fractionation.

A decrease of the level of albumin in the blood has also been shown to occur in heart failure from causes other than constrictive pericarditis (Herrmann, 1946), although this does not always imply that the production of albumin is impaired, because the total volume of plasma is usually considerably increased (Gerbrandy, 1952). The changes in blood volume and in the content of blood proteins in constrictive pericarditis are different from those in other causes of backward failure: the blood volume was only at the upper normal limit in Chambliss's patients and no increase of the level of globulin was present. The circulation time varied between 13 and 45 seconds; in 40% of the cases it was less than 24 seconds, so it can be normal as it was in our patient (8 seconds). This unexpected finding could perhaps be explained by assuming that at least a part of the magnesium sulphate is being pumped through the lungs without delay, the emptying of both ventricles not being materially impaired. The cardiac index in our patient, as calculated from data obtained during catheterization, measured

$$\frac{2\cdot4}{0\cdot73}=3\cdot31$$

per minute per square metre of body surface.

No satisfactory explanation can be given of the hypoproteinaemia in constrictive pericarditis. Apparently the production of albumin in the liver is impaired, but why are no other functions also impaired and why does constrictive pericarditis especially cause hypoproteinaemia, in contrast to other causes of chronic heart failure? The condition is quickly reversible as has been demonstrated in our patient, so it can hardly be due to fibrosis. Niggli (1950) has found a relation between the severity and length of congestive heart failure, the decrease of albumin in the blood and the presence of fibrosis in the liver, but all these patients were adults.

Finally we should like to stress that in our patient the aetiology of the constrictive pericarditis could not be tuberculous, which is at variance with several recent publications (e.g. Andrews, Pickering and Sellors (1948). The tuberculin test with 1 mg. of old tuberculin was repeatedly negative, which rules

out active tuberculosis with certainty. The histological examination of the pericardium gave no further clue as to the aetiology (J. F. Hampe).

Although the triad of Beck (1935)—high venous pressure, ascites and a quiet heart—diagnostic of chronic cardiac compression, was present in our patient, the ordinary investigations, namely, electrocardiography, fluoroscopy, radiokymography and measurement of circulation time did not confirm a tentative diagnosis of constrictive pericarditis. The unfavourable effect of digitalization and the typical changes found during catheterization led our thoughts back to the right diagnosis. Less time would have been lost had we taken the 'hard' *x*-ray pictures earlier. Therefore we wish to stress the importance of this technique, together with catheterization of the heart, in children having hypoproteinaemic oedema, ascites and increased venous pressure, which can be so easily demonstrated in the engorged veins of the neck.

Summary

A case is presented with constrictive pericarditis in a 7-year-old boy, demonstrating some atypical signs. Hypoproteinaemia and ascites were dominating. No complaints or signs of heart failure were present, with the exception of increased venous pressure, as could be demonstrated in the neck. The radiokymograph showed fair pulsations of the ventricles but the data of the pressure curves from the right auricle, right ventricle and pulmonary artery gave definite evidence of constrictive pericarditis. The presence of calcium in the pericardium could be demonstrated only on pictures taken with 'hard' *x* rays.

A successful peri- and epicardectomy (nearly total) was done, which was followed by restoration of the blood proteins in three weeks.

The association of hypoproteinaemia and constrictive pericarditis in childhood was commented upon.

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TRANSIENT DIABETES IN INFANCY

BY

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Although diabetes mellitus is estimated to begin during the period of childhood in 5 to 8% of all cases (Nelson, 1954) it is quite rare in infancy. Recovery from diabetes at any age is even more rare and the few cases that have been reported have all been in infants. The case described here had a number of unusual features.

Case Report

Ann C. was admitted to hospital on June 26, 1953, at the age of 1 month. She was the third child of healthy parents and was born at full term following a normal delivery. No abnormality had been noted at birth and the birth weight was 6 lb. 2 oz. There was no family history of diabetes. She was breast fed for three weeks and then weaned on to feeds of full-cream National dried milk. For a week before admission she had seemed rather cross but she had taken her feeds well. There had been no vomiting, she had been passing formed yellow stools and there had been no polyuria. On the evening of admission her mother noticed that 'her head seemed to have sunk in at the top' and that her colour seemed poor.

On admission she weighed 6 lb. 2 oz. (expected weight 7 lb. 6 oz.). She was pale, wasted and grossly dehydrated, the most striking feature being the deep depression of the anterior fontanelle. A small boil was present on the left thigh but no other septic lesions were visible and no other abnormal physical signs were present on systemic examination. In view of the severe degree of dehydration intravenous fluid therapy was started immediately, beginning with half-strength plasma (diluted with Hartmann's solution) of which 300 ml. was given in the first eight hours. This was followed by N/5 saline with 5% glucose, 425 ml. being given over the next 15 hours. Thus the total parenteral fluid in 23 hours was 725 ml. based on a requirement of 100 ml. per pound of expected body weight, dehydration being assessed at more than 10%. Towards the end of this period slight oedema of the eyelids and of the sacral region was noted and 19 hours after the start of the intravenous infusion she had a generalized convulsion lasting for a few minutes. Two further convulsions occurred an hour later while she was being examined. In each of these there was stiffening of the body, arching of the back and a brief period of apnoea. Apart from the slight oedema there were no abnormal findings. The anterior fontanelle was now of normal tension and there was no stiffness of the neck. Lumbar puncture was performed and bloodstained fluid under low pressure was obtained. She was sedated with chloral and, although there was no clear evidence of infection, it was considered that the initial dehydration and the subsequent convulsions were probably due to infection and treatment was started with penicillin (400,000 u. daily) and streptomycin (120 mg. daily). The baby's subsequent progress was uneventful. She fed well, gained weight steadily and convulsions did not recur. She was discharged from hospital after seven weeks, having gained over 3 lb. in weight (Fig. 1).

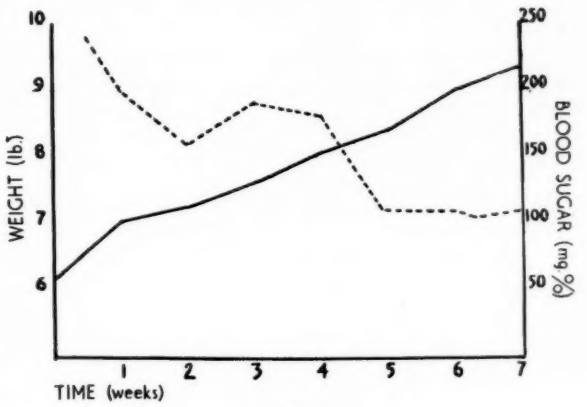

FIG. 1.

Investigations. The main interest in this patient lay in the laboratory findings rather than the clinical picture and so these are given in some detail.

Blood		
27.6.53	Urea	64 mg. %
(Before	Serum protein	8·2 g. %
treatment	Serum chloride	103 m.Eq/l. (602 mg. % NaCl)
was	Serum alk. reserve	14 m.Eq/l. (30·5 vol. % CO_2)
begun)	Plasma potassium	6·2 m.Eq/l. (25·7 mg. %)
	Plasma sodium	134 m.Eq/l. (312 mg. %)
28.6.53	Urea	38 mg. %
	Serum protein	6·5 g. %
	Serum chloride	102·5 m.Eq/l. (600 mg. % NaCl)
	Serum alk. reserve	21·8 m.Eq/l. (48 vol. % CO_2)
	Plasma potassium	5·1 m.Eq/l. (20·3 mg. %)
	Plasma sodium	133 m.Eq/l. (310 mg. %)
29.6.53	Urea	34 mg. %
	Serum protein	6·35 g. %
	Serum chloride	92 m.Eq/l. (548 mg. %)
	Serum alk. reserve	25 m.Eq/l. (56 vol. % CO_2)
	Plasma potassium	5·0 m.Eq/l. (20 mg. %)
	Plasma sodium	134 m.Eq.l. (312 mg. %)
	Serum calcium	4·75 m.Eq/l. (9·7 mg. %)
	Serum inorganic phosphate	3·54 m.Eq/l. (6·1 mg. %)

C.S.F. (xanthochromic bloodstained specimen)

29.6.53	Cells	7 leucocytes/c.mm.
	Protein	700 mg. % (globulin positive)
	Chloride	744 mg. %
	Sugar	212 mg. %
	Culture	No bacterial growth obtained

Because of the high level of the sugar a further specimen of cerebrospinal fluid was examined on June 30 and the result showed 170 mg. % sugar. Paper chromatography confirmed that the sugar was glucose. A specimen of blood taken at the same time gave a value of 245 mg. % of glucose and the urine was found to contain 0·2 g. % of reducing substances. Unfortunately this first specimen was not tested for acetone.

Over the next three weeks, while the baby was taking normal feeds of National dried milk with added sugar, the blood sugar varied from 110 to 240 mg. %. The estimations were usually done immediately before a feed, the feeding being on a four hourly schedule. Sugar continued to be present in the urine in amounts varying from 0·5 to 2·0 g. %, until July 17 when it became, and remained, sugar free. Acetone was only detected on one occasion at a time when the child was quite well and the fasting blood sugar level was 190 mg. %. No sugar was found in the bulked urine for that day. The total volume of urine passed was measured on three separate days and varied from 154 to 344 ml. The lower figure may be incorrect as the difficulties of collecting total urine specimens from female babies are considerable. The upper figure is well within the normal range for a baby of 1 month.

A glucose tolerance test was performed on July 2 with the following result:

Fasting blood sugar	130 mg. %
½ hour after 6 g. glucose ..	195 mg. %
1 ,, ,, ,, ..	245 mg. %
2 ,, ,, ,, ..	250 mg. %
3 ,, ,, ,, ..	205 mg. %

This is a typical curve of moderately severe diabetes. In view of the child's satisfactory progress and the absence of any ketonuria, treatment did not seem indicated immediately. Dietary regulation is very difficult in an infant and it was by no means certain that the diabetic state would be sensitive to insulin. In order to investigate this a glucose/insulin tolerance test was performed. The glucose tolerance test was first repeated on July 15 with the following result (Fig. 2):

Fasting blood sugar ..	152 mg. %
½ hour after 6·5 g. glucose	240 mg. %
1 ,, ,, ,, ..	263 mg. %
2 ,, ,, ,, ..	165 mg. %
3 ,, ,, ,, ..	131 mg. %

On the following day the glucose/insulin tolerance test showed:

Fasting blood sugar	120 mg. %
½ hour after 6·5 g. glucose and 0·85 u. insulin ..	232 mg. %
1 ,, ,, ,, ,, ,, ,, ..	240 mg. %
2 ,, ,, ,, ,, ,, ,, ..	82 mg. %
3 ,, ,, ,, ,, ,, ,, ..	88 mg. %

The tests were repeated one week later (July 21) with the following results (Fig. 3):

Fasting blood sugar ..	125 mg. %
½ hour after 6·5 g. glucose ..	240 mg. %
1 ,, ,, ,, ..	275 mg. %
2 ,, ,, ,, ..	165 mg. %
3 ,, ,, ,, ..	130 mg. %

And on July 22:

Fasting blood sugar	160 mg. %
½ hour after 6·5 g. glucose and 0·85 u. insulin ..	180 mg. %
1 ,, ,, ,, ,, ,, ,, ..	150 mg. %
2 ,, ,, ,, ,, ,, ,, ..	105 mg. %
3 ,, ,, ,, ,, ,, ,, ..	90 mg. %

It seemed clear from this second test that the diabetes was now sensitive to insulin, but as the baby continued to thrive and neither sugar nor acetone was present in the urine, treatment was still withheld and the level of the pre-prandial blood sugar gradually fell to normal.

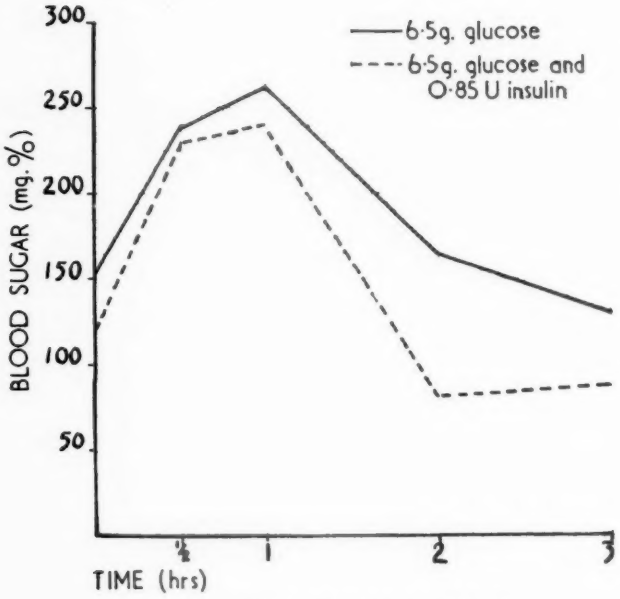

FIG. 2.—Glucose tolerance test on July 15.

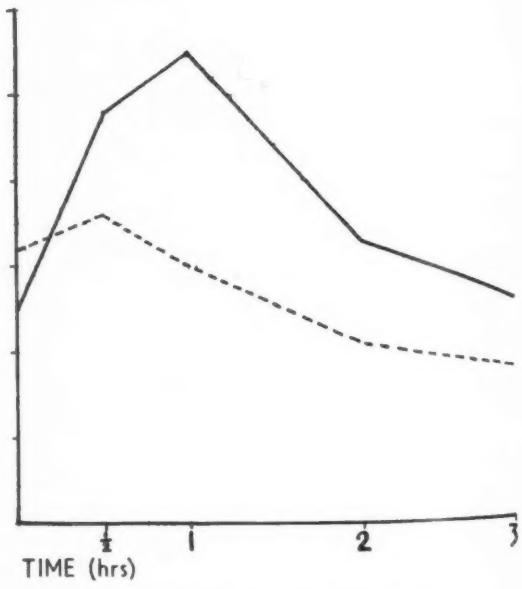

FIG. 3.—Glucose tolerance test on July 21.

Other investigations that were performed included lumbar puncture on June 30 when protein was 750 mg. % and sugar 170 mg. %. On July 1 the cerebrospinal fluid was bloodstained and the supernatant slightly xanthochromic with 135 leucocytes per c.mm (96% mononuclears) and 16,000 R.B.C.s per c.mm. No bacterial growth was found on culture.

Lumbar puncture on July 8 gave a clear colourless fluid with 8 leucocytes per c.mm., protein, 60 mg. %; globulin, positive; chlorides, 708 mg. %; and sugar, 144 mg. %.

On July 28 protein was 70 mg. %; globulin, positive; chloride, 712 mg. %; sugar, 100 mg. %.

On August 6 protein was 45 mg. %; globulin, negative; chloride, 708 mg. % and sugar 100 mg. %.

Liver function tests on July 3 gave alkaline phosphatase, 14·5 units (King-Armstrong); thymol flocculation, negative; thymol turbidity, 1·6; zinc turbidity, 2·4; serum bilirubin, less than 0·5 mg. %.

Two-way chromatography of urine on July 3 showed glycine and alanine only. No fluid was obtained on subdural puncture at two sites on both sides of the head.

A Wassermann test was negative.

Radiography of the skull and spine showed no abnormality.

Following discharge from hospital the baby continued to thrive and at the age of 10 months weighed 21 lb. 4 oz. The blood sugar half an hour after a feed was 140 mg. %. The mother was unwilling to allow the baby to be re-admitted to hospital for further studies and did not keep subsequent out-patient appointments. The family doctor reported that the child seemed perfectly well and normal in every way.

Discussion

In their critical review of the literature on diabetes in infancy, Lawrence and McCance (1931) accepted the diagnosis as proven in cases

> (1) Where definite wasting, thirst, polyuria and preferably ketonuria were present, accompanied by a heavy glycosuria (over 2%), whether the reducing substance was actually proved to be glucose or not, even if hyperglycaemia was not established; or (2) where, if symptoms and glycosuria were slight, definite and recurrent hyperglycaemia (over 0·2%) was established.
>
> On the other hand they rejected cases
>
> '(3) Which show only one or two symptoms suggestive of diabetes, in which glycosuria was only slight and might be due to lactosuria (not infrequent in infants) or to renal glycosuria. (4) Cases in Group 2 above in which hyperglycaemia is present but in which is never excessive (i.e. under 0·3%) and which may be explained by a temporary infection or disease of the central nervous system such as trauma, tuberculous meningitis or hydrocephalus.'

These criteria would now have to be modified. Both galactosaemia and the de Toni-Fanconi syndrome may present with this vague clinical picture associated with mellituria. In order to substantiate the diagnosis of diabetes mellitus it should certainly be established that the reducing substance—whether in the blood, C.S.F. or urine—is glucose and that there is a persisting hyperglycaemia. The case described above would only have fitted into Group 1 on the day of admission, for the child's subsequent progress was quite normal even though definite and persistent hyperglycaemia was established. It was never excessive, however, and did not exceed 0·3% even after a dose of glucose. Moreover the changes in the cerebrospinal fluid, which are discussed below, might be interpreted as having been due to some intracranial disturbance which would bring the case into Group 4. A high prolonged curve in a glucose tolerance test can occur in a number of conditions (Behrendt, 1949). It is found in various liver diseases, with or without jaundice, such as glycogen storage disease and fatty infiltration of the liver. There was no clinical evidence of liver disease in this patient and the liver function tests were perfectly normal. Furthermore, the impaired glucose that occurs in severe liver disease is relatively insensitive to insulin (Himsworth, 1949). Severe infections may lead to glycosuria and hyperglycaemia (Himsworth, 1949; MacLean and Sullivan, 1929) indistinguishable from that in diabetes as long as the infection lasts. It is probable that persisting diabetes after such infection only occurs in an individual who is hereditarily or constitutionally predisposed. An acute infection could not be entirely excluded in this patient but there was little positive evidence. There was only slight fever and that was on the day of admission when she was severely dehydrated; there were no abnormal physical findings apart from one small boil, the leucocyte count was normal and a blood culture was sterile after eight days' culture.

Hyperglycaemia, usually brief, may occur as a rare complication of head injury. Although there was no history of post-natal injury in the present case injury sustained at birth cannot be entirely excluded. The baby was born at home following a labour lasting eight hours. She sucked well from the start and the neonatal progress was normal. Lumbar puncture was performed on the day after admission to hospital and the fluid, which was under low pressure, was slightly bloodstained; the supernatant fluid, after centrifuging, was xanthochromic and the protein content was high (700 mg. %). A further lumbar puncture a few days later produced very little fluid, the protein content of which was between 700 and 1,000 mg. %, and a third puncture on the following day produced no fluid at all. A cisternal puncture, however,

produced a bloodstained fluid with a count of 16,000 red cells and 135 white cells (nearly all mononuclears) per c.mm. The supernatant fluid was also xanthochromic. A month later the cerebrospinal fluid flowed freely, was clear and the protein had fallen almost to normal limits. Although it was originally considered that there had been a traumatic tap at the first puncture, the subsequent changes in the cerebrospinal fluid made it more likely that there had been a subarachnoid haemorrhage which may have been present from birth. The precise relationship of this to the diabetic state remains obscure.

Diabetes resulting from a hypothalamic disturbance is usually insulin resistant but if the hyperglycaemia is persistent the islets may become exhausted and insulin-sensitive diabetes may supervene (Himsworth, 1949). The first glucose/insulin tolerance test, performed on July 16, showed no fall in the blood sugar in the first hour whereas when the test was repeated one week later the blood sugar rose only by 20 mg. % from the fasting state and at the end of the first hour it was below the fasting level. The dose of insulin used was based on the recommendation of Bridge and Mulholland (1948). They state that the normal response to a dose of 0·25 units of insulin per kg. per body weight in the glucose-insulin test is a fall in the blood sugar of 30-35 mg. % at one hour as compared with the level at this time following a standard dose of glucose. A fall of less than 30 mg.% indicates insulin resistance. It is tempting to postulate that at the earlier stage the diabetes was caused by hypothalamic damage and that later on it became insulin-sensitive due to exhaustion of the islets. However, the hyperglycaemia was never marked and it is difficult to conceive that the function of islets would become deranged in so short a time. An alternative explanation for the differing results in the two glucose/insulin tests may lie in some difference in the rate of absorption of the insulin. In the first test the insulin was injected subcutaneously in the lateral side of the thigh and in the second test it was given into the deltoid area. Although, in the original test, there was no fall in the blood sugar level in the first hour, there was a sharp fall during the second hour and this may have been due to some delay in the absorption of insulin so that it did not begin to act for a longer time.

The literature on diabetes mellitus in infancy was fully reviewed by Lawrence and McCance in 1931 and again by Schwartzman, Crusius and Beirne in 1947. The latter authors discussed 57 cases which had been previously reported and they added a further one of their own. Since 1947, 22 further cases have been described (see Table 1) including the one reported in the present paper.

TABLE 1
REVIEW OF CASES OF INFANTILE DIABETES SINCE 1947

Author	Year	Sex	Age at Onset	Family History	Ketonuria	Outcome
Whetter *et al.*	1947	M	10 months	N.G.	N.G.	Died
Guest	1948	1. F 2. M 3. M	3 months 3 months 9 days	3 siblings	N.G. + +	Died Lived, insulin Lived, insulin
Guest	1949	1. M 2. M 3. M	7 months 10 months 11 months	N.G.	N.G. N.G. N.G.	Lived, insulin Lived, insulin Lived, insulin
Recalde Cuestas *et al.*	1950	M	5 months	—	+	Died
Newcomb *et al.*	1951	1. 2. 3. 4. 5. 6. N.G.	4½ months 7 months 10 months 10½ months 10½ months 12 months	+ in 2 cases	N.G.	3 Died 3 Lived
Brødribb *et al.*	1952	1. M 2. F	11 months 11 months	+ —	— —	Lived, insulin Lived, insulin
Nawrocka-Kańska	1952	M	12 days	—	+	Lived
Wylie	1953	F	17 days	—	—	Lived, insulin
Arey	1953	M	13 days	—	Trace	Lived
Gans	1954	M	39 days	—	+	Lived, insulin
Hofman-Bang, E.	1954	M	3 weeks	N.G.	+	Lived, insulin
Present case	1954	F	27 days	—	Trace	Lived

+ = Positive. — = Negative. N.G. = not given.

Age Incidence. Both in Schwartzman's series and in the present series (Table 2) most cases occurred in the first and last quarters of the first year. Lawrence and McCance (1931) dispute the diagnosis in five of the cases in Schwartzman's series where the onset is said to have dated from birth. If these are eliminated the distribution would still be mainly at the beginning and the end of the first year.

TABLE 2

AGE AT ONSET OF DIABETES IN INFANCY

	0–3 Months	3–6 Months	6–9 Months	9–12 Months
Schwartzman *et al.* (1947)	18	10	8	14
Present series ..	8	2	2	9

Sex Incidence. In 45 cases reviewed by Schwartzman in which the sex is mentioned there are 27 males and 18 females. In the present series the sex was not mentioned in six cases and of the remainder there were 12 males and four females. Of all cases reported to date, therefore, the incidence in males is almost double that in females.

Mortality. Of the 50 cases discussed by Schwartzman in which the outcome was known, 35 died (70%). Before the introduction of insulin in 1924 the outcome was almost uniformly fatal. Of 26 cases death occurred in 23. Lawrence and McCance did not accept that the diagnosis was established in two of the cases which recovered and the outcome in the third was not known. In the period from 1925 to 1946 the mortality rate fell to 50% for the whole of the first year but it remained high for the first three months of life, seven deaths occurring in 11 cases. In the present series there were six deaths out of 22 cases (27·2%). In the first three months only one death occurred in eight cases. Newcomb, Farrell and Hand (1951) reported six cases occurring between the ages of 4½ and 12 months, three of which died. The age at onset of the fatal cases is not given and so the mortality rate for the last three separate quarters cannot be calculated.

Family History. In Schwartzman's series there was a positive family history of diabetes in 12 cases out of 28 in which it was mentioned (43%). In the present series there was a positive history in six cases out of 14 in which details are given (43%). For diabetes of all ages a hereditary factor is only present in about 25% of cases (Lawrence, 1941).

Transient Diabetes. A transient diabetic state in infancy would seem to be a very rare occurrence. Only five established cases have been published, brief details of which are given in Table 3. They have all occurred in very young infants, the oldest being 6 weeks. The onset was rapid in every case with severe dehydration. Vomiting only occurred in one case and in the others there was no excessive fluid loss from the bowel to account for the rapid dehydration. In only one case (Strandqvist, 1932) was there a definite associated infection. In the case recorded by Lawrence and McCance gangrene of the skin was present and the authors consider that this was secondary to the diabetic state. It is, however, quite possible that the gangrene was due to a severe necrotizing infection. In Ramsay's (1926) case the infant had a fever and 'an upper respiratory infection'. No details of this are given and an apparent respiratory infection is one of the diagnostic pitfalls in infantile diabetes (Newcomb *et al.*, 1951). In Arey's (1953) case also a mild pharyngitis was said to have been present but is not likely to have been the cause of the profound disturbance. The cerebrospinal fluid was examined in only one other case besides the present one and the findings in both were very similar, the protein and sugar were raised and the fluid was xanthochromic. In Nawrocka-Kanska's case (1952) vomiting was a marked feature but unfortunately the pressure of the cerebrospinal fluid was not recorded. In neither case in which the cerebrospinal fluid was abnormal was there a history of injury at birth and both infants progressed quite normally for the first two or three weeks. Nor was there a history of intracranial birth injury in the remaining four infants. Conversely, no record could be found of any infant with unequivocal evidence of intracranial injury at birth who developed hyperglycaemia. The significance of the cerebrospinal fluid changes, therefore, remains uncertain.

Despite the severity of the wasting and dehydration, marked ketonuria occurred in only one case. In two others traces of acetone were found but not until some days after the diabetic state had been recognized and when clinical improvement had occurred. The presence of acetone did not seem to be related to the height of the blood sugar level nor to the severity of the condition.

There was no family history of diabetes in any of the patients and it is not considered likely that they are 'potential diabetics' showing their trait in response to some form of stress. Ramsay's patient was reported to be in good health and fit for military service 25 years later (Arey, 1953).

Although insulin was used in the treatment of four patients the doses used were so small that it is doubtful if it was really necessary. Ramsay's patient had 0·5 units three times daily; Strandqvist gave

TABLE 3
REVIEW OF CASES OF TRANSIENT DIABETES IN INFANCY

Author	Year	Sex	Family History	Age at Onset	Highest Recorded Blood Sugar (mg. %)	Ketonuria	Clinical Features
Ramsay	1926	M	Neg.	3 weeks	263	N.G.	Rapid wasting, thirst, fever
Lawrence and McCance ..	1931	F	Neg.	15 days	600	—	Gangrene of the skin, wasting and dehydration
Strandqvist	1932	M	Neg.	6 weeks	420	—	Abscess of shoulder, wasting and dehydration
Nawrocka-Kańska	1952	M	Neg.	12 days	268	+	Vomiting, dehydration, xanthochromic C.S.F.
Arey	1953	M	Neg.	13 days	555	Trace	Rapid dehydration
Present case	1953	F	Neg.	4 weeks	275	Trace	Rapid dehydration, xanthochromic C.S.F.

1-2 units daily, Lawrence and McCance gave 1 unit four hourly and in Arey's patient the maximum dose on any day was 8 units. Although a definite clinical response was thought to occur after insulin had been given, the two babies who were not given insulin made similar, rapid recoveries. By contrast, a case of 'classical' diabetes mellitus in an infant of 39 days required 50 units of insulin hourly on the first day of treatment and was subsequently maintained on 26 units daily (Gans, 1954).

Direct studies of insulin sensitivity have not previously been reported but it is of interest that in Arey's case the blood sugar level remained high at least one week after insulin had been started and despite the marked improvement in the baby's general condition.

A review of these six cases offers little clue as to the aetiology of the condition. The evidence either for an infective basis or for a delayed result of intracranial birth injury is very slight and the very transience of the condition argues against any acute degenerative disorder. A 'toxic effect' on the carbohydrate-regulating mechanism of the brain (Strandqvist, 1932) or on the islet cells of an immature pancreas (Arey, 1953) has been postulated but begs the question as to the cause and mode of action of such a toxin. As all the known cases have recovered there has been no opportunity for morbid anatomical studies.

Although the condition is undoubtedly rare it is probable that more cases would come to light if the urine were routinely examined in every sick infant.

Summary

A further case of a transient diabetic state in a month-old baby is reported.

The literature on diabetes mellitus in infancy is reviewed.

I wish to thank Mr. J. T. Ireland for the many chemical investigations performed on this patient, and Professor N. B. Capon for his helpful criticism.

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BRITISH PAEDIATRIC ASSOCIATION

PROCEEDINGS OF THE TWENTY-SIXTH GENERAL MEETING

The twenty-sixth annual general meeting of the British Paediatric Association was held at The Old England Hotel, Windermere, from April 27 to 30, 1955.

BUSINESS PROCEEDINGS. The President, S. Graham, was in the Chair, and the following members were present:

F. M. B. Allen, Eric C. Allibone, I. McA. Anderson, John Apley, Cécile Asher, H. S. Baar, M. Bodian, R. E. Bonham Carter, F. Braid, J. V. Braithwaite, Denis Browne, W. A. B. Campbell, I. A. B. Cathie, N. S. Clark, W. R. F. Collis, T. Colver, J. Craig, W. S. Craig, E. Mildred Creak, J. Crooks, V. Mary Crosse, G. Davison, R. H. Dobbs, Eric F. Dott, D. M. Douglas, R. W. B. Ellis, J. L. Emery, P. R. Evans, D. Gairdner, W. Gaisford, W. H. Galloway, J. Gerrard, S. Graham, R. R. Gordon, E. W. Hart, J. D. Hay, W. Henderson, A. Holzel, Douglas Hubble, J. L. Henderson, J. H. Hutchison, R. Illingworth, Ursula James, Hugh Jolly, H. Everley Jones, J. J. Kempton, G. M. Komrower, R. Lightwood, P. MacArthur, D. MacCarthy, A. R. MacGregor, M. MacGregor, Helen M. M. Mackay, R. MacKeith, J. Hart Mercer, F. J. W. Millar, R. A. Miller, A. V. Neale, G. A. Neligan, D. N. Nicholson, A. P. Norman, J. N. O'Reilly, H. Parry-Williams, Clifford Parsons, C. Bruce Perry, C. Pinckney, C. T. Potter, B. Schlesinger, R. A. Shanks, Victoria Smallpeice, W. C. Smallwood. J. Forest Smith, R. E. Smith, R. E. Steen, J. Thomson, M. Thomson, J. P. M. Tizard, R. McL. Todd, C. W. Vining, D. Waterston, A. G. Watkins, T. Pearse Williams, D. W. Winnicott, Mary Wilmers, Winifred F. Young, S. Yudkin, R. B. Zachary.

The Minutes of the last annual meeting were approved.

ELECTION OF OFFICERS. The following were elected by ballot for the year 1955-56:

PRESIDENT: Professor F. M. B. Allen.
TREASURER: Dr. R. Lightwood.
SECRETARY: Dr. P. R. Evans.
EXECUTIVE COMMITTEE (for three years):
Dr. J. Vernon Braithwaite.
Dr. F. J. W. Miller.
Dr. G. Clifford Parsons.
Dr. T. Pearse Williams.
(to replace Dr. D. Court, Prof. W. S. Craig, Dr. D. Gairdner, Professor W. F. Gaisford).

ELECTION OF NEW MEMBERS. The following were elected by ballot to membership of the Association:

HONORARY MEMBERS:
Professor Stanley Graham.
Dr. Cicely D. Williams.
CORRESPONDING MEMBERS:
Dr. L. Emmett Holt, Junr. (New York).
Dr. Bronson Crothers (Boston).
Dr. G. Huët (Holland).
ORDINARY MEMBERS:
Dr. E. G. Brewis (Newcastle).
Dr. J. O. Forfar (Edinburgh).
Dr. C. Harvey (Doncaster).
Dr. W. Henderson (York).
Dr. F. P. Hudson (Southport).
Dr. J. Lorber (Sheffield).
Dr. W. H. Patterson (Manchester).
Dr. K. B. Rogers (Birmingham).
Dr. J. Thomson (Edinburgh).

The Treasurer's report was received and approved.

The report of the Executive Committee was received and approved and is printed below. Arising out of item 6, the Committee was asked to consider having a few longer communications from members or guests if there was no lecture at the meeting. Arising out of item 9, it was resolved not to publish the report on children's hospitals before the Paediatric Committee of the Royal College of Physicians of London had expressed its views.

The President made a statement about the joint meeting in Quebec, and the Hon. Secretary spoke about the International Paediatric Association meeting in Copenhagen in 1956.

There were 54 guests present including 12 from overseas.

The George Frederic Still lecture was delivered by Professor F. A. E. Crew.

Report of the Executive Committee 1954-55

1. The Association will wish to congratulate Dr. E. A. Cockayne on the award of the O.B.E.; Dr. J. L. Gamble on receiving the Moxon Medal of the Royal College of Physicians of London; Professor S. Graham on his appointment as President of the Royal Faculty of Physicians and Surgeons; Dr. W. Sheldon on being appointed a member of the Clinical Research Council; Professor

R. W. B. Ellis on being appointed a member of the Scottish Advisory Committee on Medical Research.

At the meeting of the Council of the British Medical Association on April 13, Professor Norman B. Capon, of Liverpool, was presented with the Dawson Williams Memorial Prize for 1955 in recognition of his work in child health, particularly in the field of neonatal paediatrics.

2. The Association has suffered the loss, since its last Annual Meeting, of Sir Edward Mellanby, Sir James Spence, Dr. E. M. Stephen and Dr. Harold Waller.

3. The Executive Committee has met three times since the last Annual General Meeting; the following is a summary of the matters with which it has been concerned.

4. MEETING IN QUEBEC JUNE 15-18, 1955. About 20 members will be attending, and most of them taking an active part in, this joint meeting of the Canadian and the two American societies. To commemorate the occasion the B.P.A. delegation hopes to present its Canadian hosts with a gavel carved from a surviving piece of the plane tree which stood in Dr. Mead's garden in Great Ormond Street, and which many ex-residents of the old hospital will remember.

5. INTERNATIONAL PAEDIATRIC ASSOCIATION. The next International Congress will be held in Copenhagen from July 22 to 27, 1956, under the Presidency of Professor Plum. A small sub-committee (A. A. Moncrieff, D. Gairdner, P. R. Evans) has considered and commented on the programme suggested by Professor Plum.

6. ANNUAL GENERAL MEETING. The Executive Committee discussed the value to the Association of having annual lectures ('Still' alternating with 'Windermere'). No recommendations as to the future policy were made but the matter will be reconsidered during the forthcoming year. (The endowment of the Windermere lecture ends in 1956.)

7. ARCHIVES OF DISEASE IN CHILDHOOD. The Executive Committee accepted recommendations of the Editorial Committee lengthening the term of service on the Committee to five years and altering the method of appointment of editors and committee members. They will in future be nominated by the Editorial Committee and the nominations will then be submitted to the Executive Committee.

8. HISTORY OF THE B.P.A. Dr. H. Cameron's history of the first 25 years of the Association is now in process of publication. To facilitate the task of the author of the next volume by keeping year-to-year notes, Dr. R. Mac Keith has been appointed Assistant Historian. The Executive Committee has expressed the gratitude and thanks of the Association to Dr. Cameron for his admirable work.

9. FUTURE OF CHILDREN'S HOSPITALS. The final report on this subject has been circulated to members and has been submitted to the Paediatric Committee of the Royal College of Physicians of London.

10. PROPHYLACTIC IMMUNIZATION. The report on this subject has been reconsidered, modified and submitted to the Ministry of Health, and discussed there with our representatives (J. L. Henderson, I. A. B. Cathie and R. E. Bonham Carter). No further action is contemplated until the Ministry's recommendations are known.

11. NOTIFICATION OF EPILEPTIC CHILDREN. It was considered that recommendations that epileptic children should be notified to school medical officers as soon as possible after the age of two years (Min. of Health 26/53) were open to misconstruction. A short memorandum on the subject was sent to the Ministry of Health (Sub-Committee: E. M. Creak, D. Gairdner, J. P. M. Tizard and P. R. Evans).

12. PAEDIATRIC EDUCATION QUESTIONNAIRE. This questionnaire was discussed, with considerable dissatisfaction, but no resolution was taken as it was noted that W.H.O. would provide funds for the International Paediatric Association so that a consultant could visit those who had and those who had not completed the questionnaire, for discussion.

13. OVERSEAS ACTIVITIES. The Executive Committee considered a letter from Dr. Cicely Williams advocating extension of the activities of the Association to paediatricians in the Colonies, many of whom were cut off from association with other paediatricians. The Committee concluded that such extension was desirable and the Colonial Office has been invited to send an observer to meetings, as the Ministries of Health and Education already do. The Committee offered the aid of the Association in helping visiting paediatricians to make the best use of their time in Great Britain and Ireland. It is hoped that many members will cooperate with the Hon. Secretary (to whom requests for advice will be sent) in forwarding the arrangement, and also in seeing that Commonwealth and Colonial visitors continue to be given the opportunity to attend the annual general meeting.

14. HYPERCALCAEMIA. A sub-committee (C. F. Harris, W. Sheldon, R. Lightwood, T. Stapleton) has been set up to investigate the incidence of infantile hypercalcaemia and the diets of children who develop it.

15. NATIONAL DRIED MILK. The Executive Committee has considered the policy of labelling tins of National Dried Milk, and the caloric requirements of infants. A sub-committee (J. Forest

Smith, P. R. Evans) was asked to reply to a letter from the Ministry of Health.

16. STANDING SUB-COMMITTEES. Dr. John Hay has been appointed to succeed Dr. Bernard Schlesinger on the Convalescent Homes Sub-Committee.

Progress reports have been received from the Prematurity and Growth Study Sub-committee (V. Mary Crosse, Cecile Asher). Dr. F. M. Martin's report on prematurity has now been published (*Med. Off.*, 1954, **92,** 263).

17. Other matters in which the Committee has intervened during the year have been concerned with possible appointments of S.H.M.O.s and general practitioner-consultants to paediatric posts, and of a sister not on the R.S.C.N. as matron of a children's hospital used for training for this register.

Scientific Communications

AGNES R. MACGREGOR (Edinburgh). 'The Incidence of Infection in Neonatal Deaths.' A review was made of 401 necropsies in cases of neonatal death in the Simpson Memorial Maternity Pavilion of Edinburgh Royal Infirmary during five years, from 1949 to 1953. The results were compared with those of a similar review previously made of 618 necropsies during five years, from 1939 to 1943, with special reference to the incidence and nature of lethal infection. Deaths attributed to infection in the later series were 55 or 13·7%, compared with 190 or 30·7% in the earlier series. A large increase in deaths attributed to uncomplicated anoxia and hyaline membrane in the later series suggested that better control of infection in infants of that type had not achieved a corresponding saving of life. Of deaths after the first week, 22 or 50% were attributed to infection in the later period, compared with 128 or 78% in the earlier. Gastro-enteritis and oesophageal thrush, which accounted for 45 and 19 deaths respectively in the earlier period, caused no deaths in the later, during which pneumonia was the only comparatively common lethal infection.

DR. THOMAS B. MEYER (Birmingham). 'Prematurity, Jaundice, Kernikterus Syndrome.' A study of serum and C.S.F. levels of bilirubin in full-term and premature babies and the relationship of those levels to kernikterus was made.

The study shows the curves of serum bilirubin levels on 93 babies of all weight groups and indicates that babies under 2,000 g. (4 lb. 6 oz.) have levels still rising on the sixth day, babies of 2,000-2,500 are levelling out, and levels of babies over 2,500 g. are falling by the sixth day.

Premature babies developing kernikterus have generally higher serum levels of bilirubin and the majority have levels of over 18 mg. % at the onset of signs. Kernikterus is very likely to occur where serum levels of bilirubin rise above 18 mg. %.

There appears to be no critical level of bilirubin in the C.S.F. at which staining of basal nuclei takes place and there is no correlation between the bilirubin levels in the serum and that in the C.S.F.

It is suggested that all jaundiced premature babies should have serial bilirubin estimations, the frequency of those estimations depending on the level of bilirubin and the rate of rise of that level.

It is suggested further that replacement transfusion may be effective in the prevention of kernikterus in babies whose serum bilirubin levels are above 18 mg. % or whose rate of rise is rapid.

A. C. ALLISON (Oxford). 'Haemolytic Anaemia with Poikilocytosis in Children.' Ten children with atypical haemolytic anaemia have been investigated in the Radcliffe Infirmary, Oxford, during the past few years. All showed moderate or severe haemolysis together with distortion and fragmentation of erythrocytes. Eight of the children, aged 6 weeks to 7 months, seemed to have had one syndrome, manifesting itself in varying degrees of severity. The children were acutely ill, and the haemolysis was accompanied by proteinuria, together with haemoglobinuria and an elevated blood urea level in some instances. Transfused erythrocytes, like those of the patients, were rapidly destroyed. Two fatal cases showed at necropsy widespread obstruction of the renal vessels by small thrombi consisting chiefly of blood platelets. Six other cases responded favourably to repeated blood transfusions when necessary and made spontaneous, and apparently complete, recoveries.

The remaining two cases were premature newborn children. One was a twin with a normal sibling who had a syndrome similar to that described fully by Gasser (*Helv. Paed. Acta.*, **8,** 491, 1953). Three days after birth the majority of the circulating erythrocytes had Heinz inclusion bodies; these disappeared about the sixth day, leaving distorted cells which were removed from the circulation. During the period of haemolysis the child received blood transfusions, the transfused erythrocytes cells surviving normally, and a complete recovery was made. The other child developed kernikterus and died on the fifth day of life. The only medication which these two babies had received was 'synkavit' in relatively large doses (30 mg. and 20 mg./day) and it is suggested that the administration of this substance may have been a factor in the aetiology of the haemolysis.

Injections of 'synkavit' and other vitamin K analogues into rats in doses of the same order of magnitude produce severe haemolysis and haemoglobinuria when the animals are deficient in vitamin E. Many newborn infants, in particular premature babies, are known to be deficient in this vitamin, and because of their poor liver function they are susceptible to cumulative action of noxious drugs.

It is therefore concluded that vitamin K analogues are potentially haemolytic and should not be given in large doses or over a long period of time to newborn children.

ROY ASTLEY (Birmingham). 'Ciné-radiography in Paediatrics.' The conventional method of ciné radiography involves the photography of the fluorescent screen. This requires a heavy loading of the *x*-ray apparatus and a high dosage of radiation to the patient.

These disadvantages have been considerably reduced by the development of the image amplifier which produces a screen picture reduced in size but much increased in brightness. A ciné camera, linked to the *x*-ray generator so that each ciné frame is exposed as an individual radiograph, is used to photograph the amplified image. Disadvantages are the restricted field (at present a 5-in. circle) and limited definition; the gain of a sense of movement overcomes this latter failing and the field is adequate for many paediatric examinations. For analysis the films are shown as endless loops by a special projector that allows slowing or stopping of the picture.

(The following examples of the use of ciné radiography were shown: slow-motion angiocardiography at 32 pictures a second in tricuspid atresia, Fallot's tetralogy, atrial septal defect; barium examination in gastro-oesophageal incompetence; disordered swallowing in thrush oesophagitis; urethography; portal venography in the Banti syndrome.)

The development of the apparatus was made possible by the Endowment Research Fund of the Birmingham United Hospitals.

J. D. HAY (Liverpool). 'A Surgical Treatment of Atrial Septal Defects.' Ten patients with atrial septal defects, eight children, aged 7 to 16 years, and two adults, aged 21 and 35 years, were treated surgically. Their condition before and after operation was described, the post-operative periods being from one to eight months. The diagnosis was confirmed in nine cases by cardiac catheterization and in one by angiocardiography. Three had developed pulmonary hypertension before operation.

Two patients died following the operation. In the other eight, surgical closure of the defect was thought at operation to be complete or almost complete in six. Following the operation the right atrium appeared smaller on radiography in four; pulmonary vascularity appeared to be less in four; the P wave in lead 2 of the E.C.G. was smaller in four; the systolic murmur in the pulmonary area ceased or became softer, suggesting a reduced blood flow through the pulmonary artery, in six; and exercise tolerance was increased in three of the five in whom it was reduced before operation. One or more of these changes occurred in every patient whose defect was repaired. It was therefore considered that in some cases at least of atrial septal defect the surgical procedure adopted achieves immediate satisfactory closure of the defect. The permanency of such closure and its ultimate value must await a long-term follow-up which should include recatheterization of the heart.

HUGH JOLLY (Plymouth). 'The First Three Years as a Provincial Paediatrician.' The work of the paediatrician in London and the Provinces was critically compared in an attempt to reduce the gulf between them. The greatest loss sustained by the lone provincial paediatrician was the reduction in academic atmosphere and the absence of student-teaching, though there were other compensations. In the provinces it was easier to develop a close liaison with the general practitioners and the Public Health Department, and because of this and the compactness of the area one could practise child health in all its aspects rather than treat sick children in hospital. A further compensation was the greater opportunity for combined clinical work with colleagues in other specialities. The paediatrician, more than any other consultant, was in a position in which he could serve a community.

There should be more interchange of staff between teaching and provincial hospitals and this should certainly include the registrar but could also include the students. These might spend part of their training in small groups attached to a provincial paediatrician.

The newly appointed provincial paediatrician was advised to concentrate his work in one hospital and immediately to start a premature baby unit if none existed. He should not undertake peripheral work until his base was secure.

The conclusion was reached that whatever the particular interest of the young paediatrician he should spend at least five years in the provinces as an essential part of his training.

MILDRED CREAK (London). 'Child Psychosis.' Eighty-seven cases of psychotic illness in early childhood are reviewed. Only eight are able to attend normal school and at least one of these can only do so receiving special consideration. The others are either in special (E.S.N.) schools, or institutions for the mentally defective, or awaiting admission. Some are at home being personally cared for by their parents, but many of these appear likely to be suitable for such admission at a later date.

It appears certain that this is not a homogeneous clinical group. The criterion of inclusion has been a period of apparently normal development followed by a cessation of development which especially affects speech, social capacity, and learning. Motor agility and fine co-ordination remain good, although movements may become aimlessly repetitive or stereotyped. The essential feature is the way in which the child withdraws into himself.

Whether organically (i.e. structurally) determined, as it seems to be in some cases resembling a post-encephalitic illness, or whether emotionally determined, as when the regression follows on a situation of grief or tension, this clinical group appears to be one which contributes significantly to the so-called mentally defective population.

HENNING ANDERSEN (Copenhagen). 'Some Changes in Mesenchymal Tissues in Hypothyroidism in Children.' Previous reports and recent findings show that increased amounts of metachromatic ground-substance and highly granulated mast cells, hyperkeratosis oedema and fibril changes could be demonstrated in skin biopsies in 21 out of 39 hypothyroid children, untreated or off treatment at the time. These changes, too, were found in 10 of 22 probably hypothyroid, but in none of 75 euthyroid children. The changes followed the medication or withdrawal of thyroidin.

Provided that the skin changes are due to an action of thyrotrophin they would not be expected in cases of pituitary hypothroidism. Simultaneous skin biopsies and serum thyrotrophin determinations, together with

radioactive iodine studies on these children seemed to support this view.

From examination of bone tissue, especially the spine, of 14 cases of untreated or very insufficiently treated cases of hypothyroidism, aged from 3 months 16 years, the *x*-ray findings were shown. The histochemical findings will be reported later. Dysgenesis of the spine could be demonstrated in all cases, following closely the retardation in bone-age and the degree of epiphyseal dysgenesis. Localized deformities were found in four cases.

G. A. NELIGAN (Newcastle-on-Tyne). 'The Effect of Intramuscular Streptomycin in Cases of Hyperchloraemic Renal Acidosis.' Twenty-one infants suffering from hyperchloraemic renal acidosis were treated with intramuscular streptomycin, 20 mg. per lb. body weight daily, for a period of three weeks. The full diagnostic criteria included a serum alkali reserve under 35 ml. CO_2 %, and a urine *p*H above 6·75, on at least two occasions. Eleven cases fulfilled these criteria completely: their average rise in alkali reserve during treatment was 20 ml. CO_2 %, and their average rise in weight was 18 oz. But five of them showed an immediate subsequent biochemical and clinical relapse and required to be treated with alkali; the remaining six did not require further treatment, although some showed a temporary biochemical relapse. Another 10 cases did not quite fulfil the criteria in all respects, and evidence was produced to show that these were probably milder cases. Their initial response to streptomycin was as satisfactory, and only two required any further treatment. It was concluded that streptomycin can be relied upon to produce marked clinical and biochemical improvement in this disease, probably by some unexplained direct action upon the renal tubules, but that its effect ceases with cessation of treatment. It was decided to make use of the initial dramatic effect in future by giving streptomycin for one week before starting an appropriate dose of alkali, and this worked very well in the only case of the disease encountered since this decision was reached, over a year ago.

K. W. CROSS, J. P. M. TIZARD and D. A. H. TRYTHALL (London). 'The Metabolic Response of Newborn Infants to Varying Concentrations of Oxygen.' An investigation was made into the metabolic response of newborn infants to a low oxygen mixture (15% oxygen). The infant was placed in a body plethysmograph and a mask placed over its face through which either air or the 15% mixture could be drawn with a suction pump. With the infant asleep, samples were collected over 10-minute periods consisting of a mixture of expired air plus the original gas mixture. Collection was made in 20 l. aspirators over a saturated salt and glycerine mixture and analysed for oxygen and carbon dioxide content in a research Haldane apparatus. Thus the oxygen consumption and carbon dioxide output were calculated and from these the respiratory quotient.

Three groups of babies were examined aged 0-14 days: (*a*) Eleven full-term infants who had two 10-minute period samples both on breathing air with a five-minute gap in between; (*b*) 16 full-term and (*c*) 16 premature infants who had an initial 10 minutes' sample on air then 15 minutes on 15% oxygen during the last 10 minutes of which a sample was taken.

The infants did not over-breathe during the collection period on 15% oxygen and there was a rise in respiratory quotient which varies from 0 to 15%, increasing with age. There was, however, a marked and significant fall in oxygen consumption of about 17%. This appears to be an observation not previously described.

WALTER HENDERSON (York). 'Congenital Defects of the Skull with a Consideration of the Prognosis for Cranial Meningocoele.' A short series of cases of midline defects of the skull was described and illustrated with lantern slides. The great variation in size, shape and position of the bone gap in cases of cranial meningocoele was noted.

In contrast the radiological appearances in congenital dermal sinus with intracranial dermoid cyst were demonstrated, and the need stressed for accurate radiology when this diagnosis was suspected.

Discussion of cases of cranial meningocoele showed that while a severe defect may preclude operative help there is much to be said for early operation in many cases. Follow-up of some cases for seven years showed that normal development was possible after operation and it was noted that in no case in the series had the bone gap been filled in with bone substitute.

The need for a full discussion with the parents of the implications and significance of a cranial meningocoele was particularly stressed.

This series demonstrated the possible association of midline skull defects with other congenital defects, especially congenital defects of the cervical vertebrae; also with hydrocephalus, microphthalmia and craniostenosis.

THOMAS STAPLETON and WILLIAM B. MACDONALD (London). 'Balance Studies during the Treatment of Idiopathic Hypercalcaemia.' Study of three cases of idiopathic hypercalcaemia of infancy has shown ways in which the serum calcium can be lowered.

A synthetic calcium-free milk caused a fall in the serum calcium and a negative balance, but the negative balance became much more marked when a calcium-free cereal, which had a high inorganic phosphorus and phytic acid content, was added to the diet.

Cortisone caused a fall in serum calcium, but the level rose again when the cortisone was discontinued. No significant changes in the phosphorus or magnesium balance were found.

R. M. FORRESTER (Manchester). 'The Dental Changes in Kernikterus.' Published in full on page 224.

The following also read papers:

DENIS BROWNE (London). 'Analysis of Results of the First Hundred Cases of Swenson's Operation (Recto-sigmoidectomy) for Hirschsprung's Disease.'

RONALD EDWARDS (Liverpool). 'Evolution of the Operative Procedure Adopted for Atrial Septal Defects.'

BOOK REVIEWS

Recent Advances in Paediatrics. Edited by DOUGLAS GAIRDNER. (Pp. 469; illustrated. 42s.). London: J. & A. Churchill. 1954.

This book is full of useful and important information, and Dr. Gairdner has been fortunate in his team of contributors.

The last 15 years have seen many new advances in paediatrics, and during this period our conception of certain well-known diseases, such as coeliac disease and Hirschsprung's disease, has undergone considerable change. It is therefore particularly apt that this book should appear now, at a time when a review of this field of medicine is really called for. The chapters on establishment of respiration and the care of the newborn infant, which are contributed by Dr. Gairdner himself, are both excellent, and the common sense shown in the discussion of such subjects as umbilical hernia and circumcision is most refreshing. The chapter on prematurity includes a full discussion of retrolental fibroplasia and the other relatively rare but important complications met with; this is very well done, but it would have been useful if the higher vitamin D and iron requirements of the premature infant had been stressed, although these are generally known. There is a most authoritative account of haemolytic disease of the newly born, but there are surely cases where a simple transfusion is called for in this disease, or when for some reason an exchange transfusion is impracticable, and it would have been helpful if this had been mentioned. A discussion on infant feeding is apt to be a rather dull and stale affair, but it is made interesting and stimulating in the section devoted to it in this book.

Oesophageal atresia and hiatus hernia are well discussed, but in the chapter dealing with Hirschsprung's disease, which is good, it is a little surprising to find that among other causes of chronic constipation no mention is made of a fissure or shallow ulcer in the anal region, for such conditions, producing pain and spasm as they do, are surely the commonest cause of constipation in young children and deserve to be more frequently emphasized.

The aetiology of gastro-enteritis is fully considered, and its treatment, especially the management of dehydration and electrolyte depletion, is gone into very well.

Immunization against infectious disease is dealt with in a most helpful manner.

Coeliac disease and fibrocystic disease are discussed, each in a chapter to itself, but it is a pity that a fuller and more vivid clinical picture of the latter condition was not drawn.

The article on intersexuality and the adrenogenital syndrome is difficult reading for those not well founded in endocrinology, but it is full of information.

The chapter on sudden death in infancy is most interesting, and the subject of congenital heart disease is well done.

The other chapters, which include cerebral palsy and tuberculosis, are all good and well worth reading.

This book should prove a valuable addition to the library of those interested in paediatrics, more especially if they already have experience in this field of medicine. It does not claim to be exclusive, but it is still a most useful book to possess. It is well produced, illustrated and indexed, and the references given in each chapter are very full.

Pediatric Diagnosis. By MORRIS GREEN and JULIUS B. RICHMOND. (Pp. xvii+436. 50s.) London: W. B. Saunders. 1954.

This book sets out to be a practical manual for students and practitioners to be used, the authors claim, as an aid to early diagnosis 'at the bedside or in the office'.

The patient's approach to his doctor is through his symptoms and the doctor's to his patient via the clinical examination; so the book deals almost entirely with these two aspects of medicine. After a brief introduction there is a long section on the clinical examination, with an evaluation of all the possible physical signs and of a great variety of laboratory aids to diagnosis. A second long section is made up of a classified list of almost every symptom known, with all the conditions that might cause them. This section is highly systemized, and every device of heading, sub-heading, Roman numerals, capital letters, small letters and bracketed numbers has been used to facilitate a rapid search for the appropriate condition.

The book is undoubtedly a difficult one to use, the layout being unfamiliar to the English student, who is at first almost repelled by the arrangement. One can, for instance, choose between 80 causes of vomiting, 41 of splenomegaly and over 90 of cyanosis. Nevertheless, it contains a great deal more accurate and easily obtainable factual information than most medical textbooks twice its size and, in an obscure and difficult case could well be considerably more helpful. Whether it is possible or not to come to an accurate diagnosis by posting from reference to reference will depend largely on the reader. On some shelves this book might become the most well-thumbed manual of paediatrics; on others it may well remain untouched for years.